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Formation of a Sydno[3,4- *a*]indolone and Reactions Thereof

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FORMATION OF A SYDNO[3,4-*a*]INDOLONE AND REACTIONS THEREOF

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By

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Ryan Christopher Vikan ENTITLED Formation of a Sydno[3,4-a]indolone and Reactions Thereof BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

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Abstract

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Formation of a Sydno[3,4-*a*]indolone and Reactions Thereof

In the present work, a synthetic route to the formation of a sydno[3,4-*a*]indolone was explored in the hope of attaining the first example of a fused-ring sydnone with an sp^2-hybridized bridge. Formation of this product and exploration of its chemical behavior was anticipated to be of particular interest to the formation of NO-releasing prodrugs.

A direct synthetic pathway to yield the target sydnoindolone starting from 3-(2-methoxycarbonylphenyl)sydnone and reaction with a base was proposed and explored. Attempted formation and isolation of the target sydnoindolone proved impossible under a variety of different conditions, undoubtedly due to the instability of this intermediate. To "work around" this proposed instability, a “trapping” protocol for the sydnoindolone was explored. Thus, the ester starting material was treated with LDA (or LHMDS) at -78°C for 10 minutes whereupon another organolithium base was added, with the expectation that the latter would intercept the intermediate sydnoindolone. Indeed, when this approach was utilized with methyl, phenyl and butyl lithium, the corresponding fused-ring sydnoindoles were formed in yields ranging from 15-44%. A brief exploration of optimization of the process was explored using methyl lithium as the second base /

nucleophile. The relative success of this approach led to extension to other nucleophiles such as a Wittig and three Grignard reagents. The former did not provide the desired alkenyl product but the latter did form the corresponding fused-ring sydnoindoles, albeit (where comparison could be made) in lower yield than from the use of the organolithium species.

With this new avenue to the fused-ring sydnoindoles in hand, it was elected also to further test their reactivity. Unfortunately, reactions (acids, base followed by alkyl halide) carried out upon 5-hydroxy-5-methylsydno[3,4-*a*]indole as the test molecule in attempts to affect the alcohol moiety proved to be futile as recovery of the sydnoindole resulted. However, preparation of 5-hydroxy-5-vinylsydno[3,4-*a*]indole from the use of vinyl magnesium bromide as the "trapping" reagent provided a more reactive species, especially under acidic conditions. Reactions of this new sydnoindole with acids yielded surprisingly stable, fused-ring alkenyl sydnones with an sp^2-hybridized bridge and, accordingly, these valuable findings stimulated an attempt to increase the efficiency of the process leading to the formation of 5-hydroxy-5-vinylsydno[3,4-*a*]indole. It was conjectured that the target molecule would be available directly from 3-phenylsydnone by a known dilithiation protocol followed by treatment with methyl acrylate and, indeed, this process was more successful, though the overall yield was still very low.

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Acknowledgements

I would like to express my sincerest gratitude to my research advisor Dr. Kenneth Turnbull for his guidance and support over the past few years I have worked for him. The knowledge that he has shared with me will continue to aid me in years to come.

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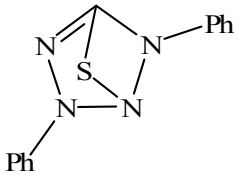
Introduction

Foreword

In 1882, Emil Fischer[1] reported that the oxidation of dithizone yielded a crystalline orange compound that he entitled dehydrodithizone and to which he assigned the bicyclic structure **1**. As more analytical techniques became available, a better understanding of this species was gained. Baker, Olis and Poole[2, 3] coined the term mesoionic (mesomeric/ionic) in describing the monocyclic, dipolar nature of compounds such as dehydrothizone and, in 1955, the molecule was determined to be the first known mesoionic species and assigned the dipolar, monocyclic structure **2**.[4]



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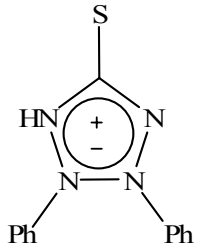


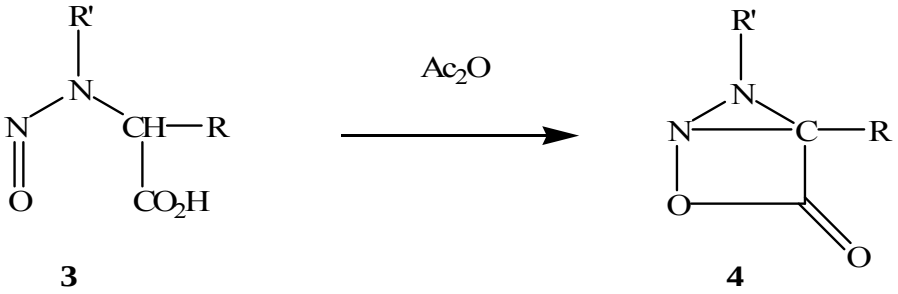
2

Although dehydrothizone was the first mesoionic compound discovered, sydnones have been the most investigated. Sydnones are small, aromatic and have a unique variation in electron density around the ring. They have been studied extensively in terms of their chemical, physical and biological properties and applications. There have been numerous reviews on mesoionic compounds, including sydnones,[5-12] as well as several M.S. Theses from this laboratory that encompasses the discoveries related to sydnones covering 1989-2005.[13-23] The review that follows will serve to acquaint the

reader with some of the more important features of previous sydnone work, as well as to summarize the pertinent sydnone chemistry that has occurred from 2005-2007.

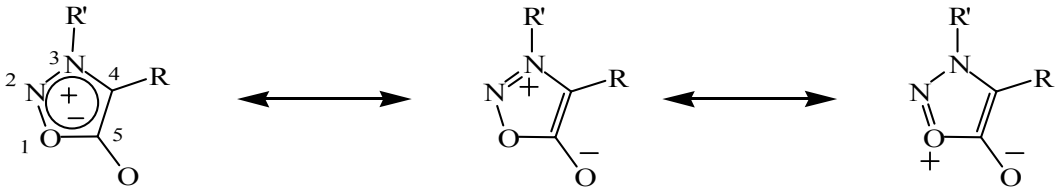
Historical

Earl and Mackney[24] discovered that treatment of N-nitroso-N-phenylglycine (**3**, R=H, R'=Ph) with acetic anhydride afforded a neutral, anhydro derivative to which the bicyclic structure **4** (R=H, R'=Ph) was assigned. From this basic structure, several analogs were synthesized and named "sydnones" due to their preparation in Sydney, Australia.

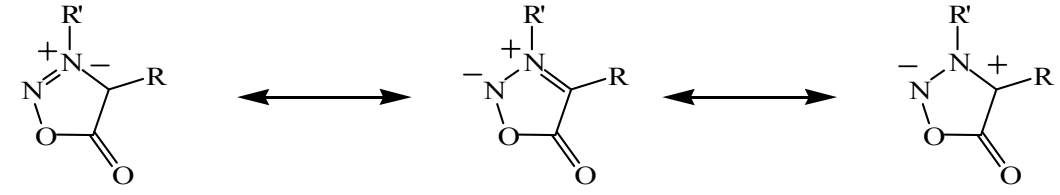


3 **4**

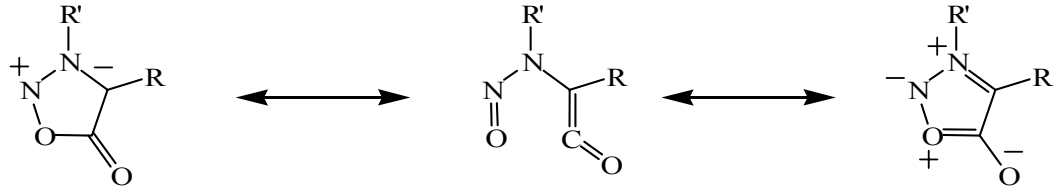
Baker, Ollis and Poole[2, 3] showed that the assigned structure **4** for sydnones was incorrect and that they were actually monocyclic, dipolar oxadiazolone derivatives with many resonance forms (**5**a-h) contributing to the resonance hybrid; designated using representation **5**. The authors decided that due to their unique characteristics, sydnones needed to be placed in their own class, namely mesoionic (mesomeric/ionic). In order to fit this classification, a molecule must: (1) contain a fully delocalized positive and negative charge in the molecule; (2) be planar and contain a five-membered heterocyclic ring with an exocyclic atom or group capable of bear a considerable amount of charge density; and (3) possess a considerable resonance energy.[4]



5 **5a** **5b**



5c **5d** **5e**



5f **5g** **5h**

These three characteristics help in distinguishing mesoionic compounds from formally related dipolar species such as ylides and zwitterions where a great deal of charge localization is observed. In the mesoionic systems, the charge distribution is delocalized and no single resonance form can be drawn.

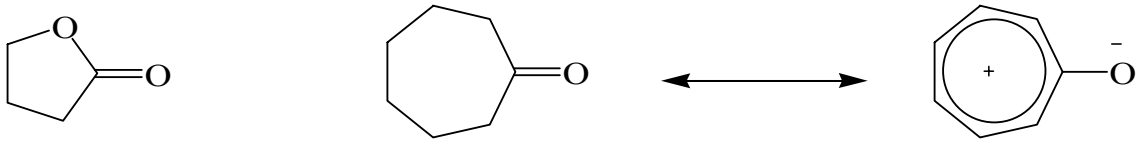
Sydnones are 1,2,3-oxadiazole derivatives: however, it appears that sydnones are the only derivatives of this class that are cyclic in nature since 1,2,3-oxadiazoles are known to be open chain, alpha carbonyl diazo derivatives. Therefore, the name "sydnone" has become the most common way of describing these compounds and, indeed, is used by Chemical Abstracts as a way of grouping these oxadiazole derivatives.

Physiochemical Properties and Electronic Structure

Generally, sydnones are stable compounds with considerable polarity. Arylsydnones are usually crystalline solids while alkylsydnones are often liquids or low-melting solids, which can be distilled *in vacuo* without much decomposition. Sydnones are soluble in organic solvents except for the nonpolar solvents such as ether and hexanes. They are also insoluble in water unless polar functional groups are present on the molecule.

Infrared spectroscopy shows two distinct characteristics for sydnones: a strong carbonyl stretch at ~1730-1760 cm^{-1} and a C-H stretch absorption with medium intensity at ~3150 cm^{-1} for the C-4 ring position (when present). [25-28] The C-H absorption for the C-4 position (when present) is different from what is normally expected for an alkyl or aryl substituent or from an epoxide with similar ring strain, which shows the absorption around 2900-3050 cm^{-1}. This makes this absorption useful in determining whether or not the C-4 position is substituted in a sydnone with an unresolved structure. In the NMR spectrum, the C-4 position usually appears between 6.5-7.5 ppm depending upon solvent.

Due to Fermi resonance, the strong carbonyl stretch is sometimes split. [29, 30] When comparing this stretch to congeneric carbonyl species, such as a γ-lactone (**6**) (which absorbs at 1770 cm^{-1}) and tropone (**7**) (which absorbs at 1638 cm^{-1}), one may conclude that the exocyclic C=O bond at the sydnone C-5 position is closer in length to that of a double bond rather than a single bond.

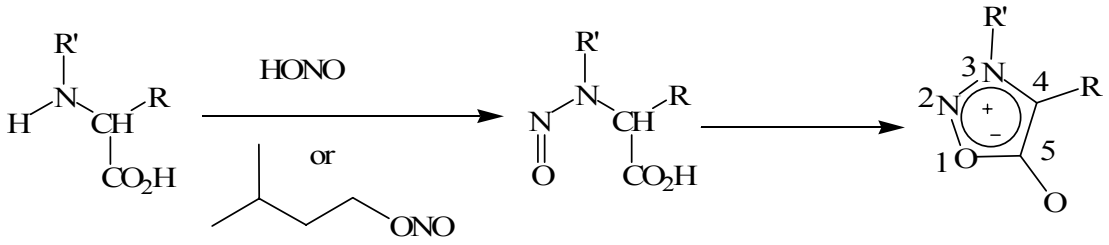


6 **7**

Analysis of various 3-substituted and 3,4-disubstituted sydnones by X-ray crystallography has shown that the C=O bond is closer in length to that of a double bond.[29, 30] Integrated absorption measurements, however, suggest that a high degree of carbonyl bond polarization, not bond strength, is responsible for the relatively high energy of absorption. Also, molecular orbital calculations and vibrational force constants from vibrational spectra indicate a π-bond order for the sydnone carbonyl lower than those for alicyclic esters,[31] which gives support to the argument that contributions from other vibrational modes cause the sydnone carbonyl group to absorb at a higher than anticipated frequency. Theoretical and spectroscopic studies have shown that protonation of a sydnone moiety occurs at the exocyclic oxygen.[32-36] This work compliments earlier work in which bond orders and charge densities of various sydnones were correlated to the calculated and observed dipole moments and the observed UV maxima.[37, 38] These studies thereby support the contention that substantial charge density resides on the exocyclic oxygen.

Synthesis

The only general route to sydnones is *via* the cyclodehydration of N-substituted N-nitroso-α-amino acids (*cf.* **3**). The R substituent can be alkyl, aryl, or a hydrogen, but the R' substituent must be alkyl or aryl; since, if the R' is a hydrogen, prototropy occurs, yielding a neutral species. The preparation of a N-nitrosoamino acid **3** involves the nitrosation of a N-substituted glycine **8** with nitrous acid or, if non-acid conditions are needed, isoamyl nitrite in dimethoxymethane.[39]



8 **3** **5**

Earl and Mackney originally used acetic anhydride at room temperature for six days for the cyclodehydration step. However, the method of choice has been the cyclization with trifluoroacetic anhydride (TFAA), which occurs rapidly (<15 minutes) at low temperature (-5°C to 0°C) in high yields. Other strategies explored have been: heating in acetic anhydride or thionyl chloride, treatment with phosphorous pentoxide, acetic anhydride at room temperature facilitated by ultrasonification,[40] haloiminium salts,[41] N,N- dimethylchlorosulfitemethanium chloride,[42] and 2-chloro-1,3-dimethylimidazolinium chloride.[43] The use of TFAA remains the most widely employed

method due to its efficiency, speed and consistency even though it has a greater cost than some of the other methods.

Chemical and Biological Behavior

There has been a considerable effort to show that the sydnone ring possesses a distinct aromatic nature and a dichotomy in electronic effects. An intrinsic property of an aromatic system is to undergo electrophilic aromatic substitutions, and it has been shown that sydnones undergo electrophilic substitution at the C-4 position of the ring (*cf*. **5**, R=H).[44] Such reactions on sydnones include halogenation, nitration, acylation, and sulfonation. The high regioselectivity of these reactions (even when an aryl group is present at the N-3 position) has been attributed to two factors: (1) the considerable partial negative charge that resides at the C-4 position appears to activate this position; and (2) the considerable partial positive charge that resides at the N-3 position seems to deactivate the juxtaposed aryl ring. In cases where activating groups are attached to the aryl ring, however, the aryl ring moiety can successfully compete for the electrophile, which is realized in both halogenations and nitrations.[45, 46]

Sydnones have also been studied in their uses as precursors to hydrazines,[24] as 1,3-dipoles in cycloaddition reactions,[47-48] electrolytic solvents for non-aqueous batteries[49] and their ability to aid in micelle production in molecular aggregation.[50] Additionally, sydnones have a very attractive aspect in the biological properties they possess, which include anti-fungal, anti-inflammatory,[51] analgesic, anti-bacterial and anti-tumor activities.[52] Sydnones also possess liquid crystal properties,[53] have been incorporated into azo dyestuffs[54-57] and have been tested for use as lithium battery electrolytes.

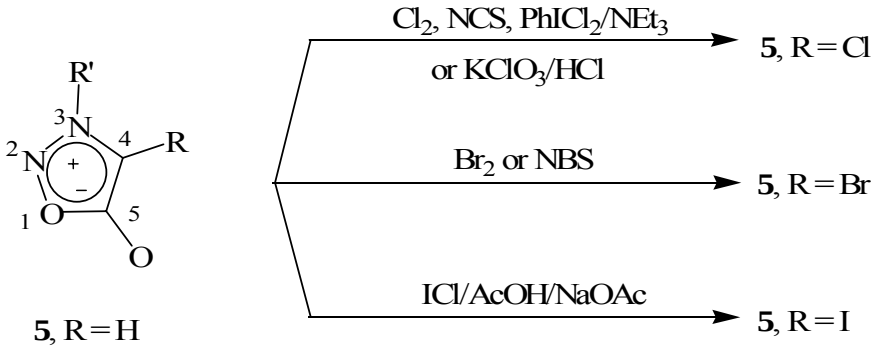
Reactions of Sydnones

I. Electrophilic Aromatic Substitutions of Sydnones

Sydnones are able to undergo electrophilic aromatic substitution at the C-4 position when there is a proton present at this position (*cf.* **5**, R=H). The electrophiles that are typically used for aromatic substitutions can be employed with sydnones due to the existence of a considerable negative charge density at the C-4 position. Halogenation, nitration, acylation, and sulfonation will be discussed in the following pages.

A. Halogenation and Nitration Exclusively at the C-4 position

Chlorinated sydnones (*cf.* **5**, R = Cl) can be obtained through the treatment of **5** (R = H) with chlorine,[58-60] potassium chlorate in moderately concentrated HCl,[61] dichloroiodobenzene with triethylamine,[62] or N-chlorosuccinimide (NCS).[63] Reactions of 3-phenylsydnone, **5** (R = H), with bromine[58-60] or N-bromosuccinimide (NBS)[63] yield the 4-bromosydnone **5** (R = Br). Iodinations of sydnones at the C-4 position have been achieved using iodine monochloride in acetic acid at room temperature.[64] In more recent work, it has been shown that DBH (dibromohydantoin) can conveniently promote the bromination of these sydnones to their 4-bromo substituted congeners (**5**, R=Br, R'=Ar) in excellent yields in DMF at room temperature.[65]

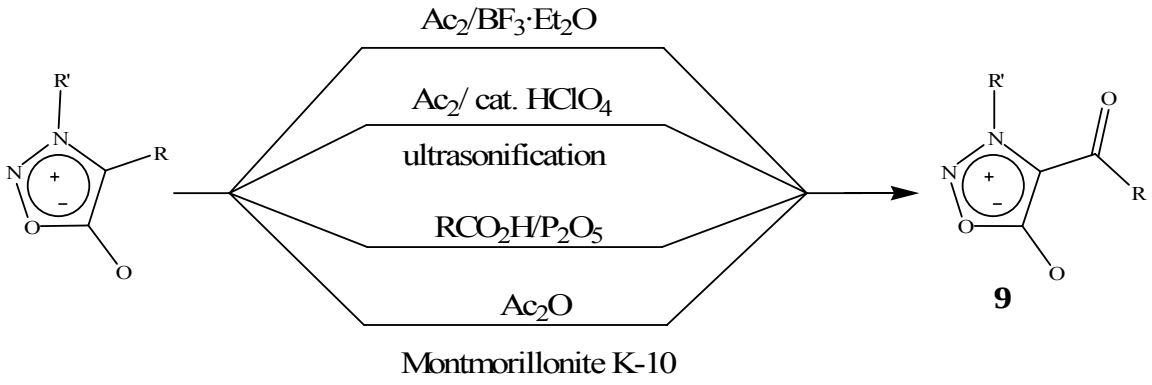


The ease with which sydnones could be brominated led to the postulation the 4-bromo moiety (*e.g.* in **5**, R = Br) could be used as a protecting group for the sydnone ring.[66] Sodium borohydride or sodium dithionite in methanol[67] or activated zinc under ultrasonification[68] have been shown to be effective in the debromination of the C-4 position in a regioselective fashion. The drawbacks associated with these methods include the capability of the sodium borohydride to react with pendant functional groups (especially carbonyl compounds), the effects of steric factors with the use of sodium dithionite, and the inefficiency of the ultrasonification method when strong electro-withdrawing groups are present. The method of choice for the debrominations becomes the use of sodium sulfite,[69] as it suffers from none of these drawbacks. All of these debromination methods are complementary and are useful tools in the chemistry of sydnones.

Due to the need for strongly acidic conditions during nitrations, this particular substitution reaction has hardly been investigated with sydnones. However, reaction of potassium nitrate in sulfuric acid at -5°C with 3-phenylsydnone (**5**, R = H, R' = Ph) affords the relatively unstable 4-nitro derivative (**5**, R = NO_2, R' = Ph).[70]

B. Acylation, Carboxamidation, and Sulfonation at the C-4 position

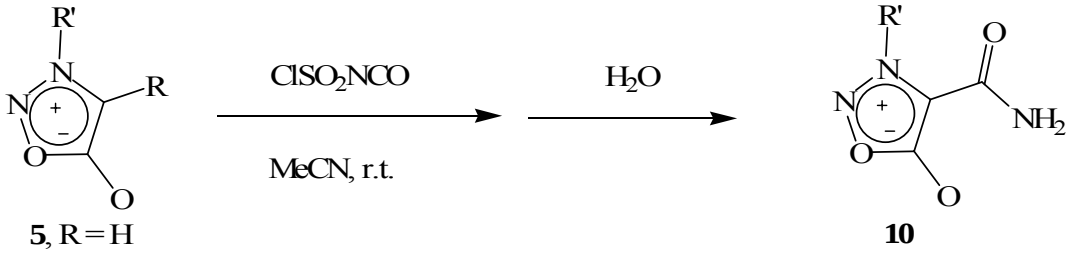
It had been reported[71] that it was not possible to acylate 3-phenylsydnone, **5** (R = H, R' = Ph) with either acetic anhydride or benzoyl chloride. However, in the presence of a Lewis acid catalyst, Yashunskii showed that the 4-acetyl derivative, **9** (R=Me, R'=Ph) could be obtained *via* the use of acetic anhydride and boron trifluoride etherate.[72] In more recent work, Tien and coworkers have acylated various substituted sydnones using acetic anhydride and $HClO_4$ or H_3PO_4.[73] Greco and coworkers[74] have also obtained the desired acylated sydnones by heating various 3-substituted sydnones in the presence of a carboxylic acid and P_2O_5. However, it was noted that neither aryl nor aralkyl acids reacted, thus limiting the scope of this process.



In a more recent method, it has been shown that 4-acylsydnones can be prepared in a two-step process from a cuprosydnone (*cf*. Metallation of Sydnones section). Tien and coworkers[75] have shown that ultrasonification of 3-substituted sydnones in the presence of acetic anhydride and a catalytic amount of perchloric acid will afford the 4-acylated derivatives quickly, in moderate yields. The 4-acetyl derivatives of 3-substituted sydnones have also been obtained using acetic anhydride with a catalytic amount of Montmorillonite K-10 at elevated temperature.[76] This method is useful since the catalyst can be removed easily and disposed of; however, one disadvantage is that the

method is sluggish or unsuccessful with compounds containing electron-withdrawing groups on the aryl-ring *ortho* to the sydnone.

In the past, 4-carboxamido sydnone species **10** have been made by a multi-step process involving abstraction of the sydnone ring proton with butyllithium, treatment with carbon dioxide, and the subsequent conversion to the acid chloride followed by reaction with ammonia. More recently, a new method of carboxamidation at the sydnone 4-position has been developed.[77] Using chlorosulfonyl isocyanate in acetonitrile at room temperature, Turnbull, Gross, and Hall prepared 4-carboxamido sydnones in good yield from a variety of 3-substituted sydnones.

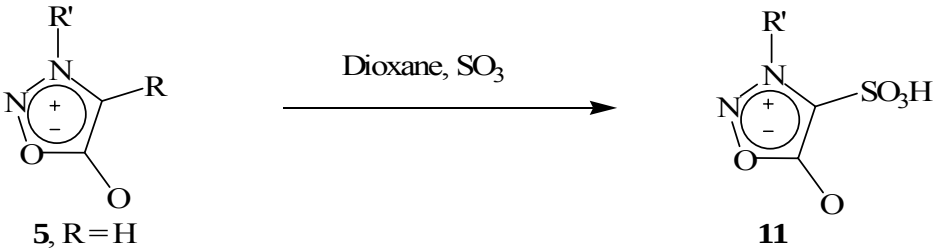


5, R = H

10

R' = Ph, 3-$MeOC_6H_4$, 4-ClC_6H_4, 2,3-$Me_2C_6H_3$

Yashunskii and coworkers reported the direct sulfonation of a variety of 3-substitued sydnones.[78] They showed that the treatment of sydnones **5** (R=H) with dioxane-sulfur trioxide complex in CH_2Cl_2 at 20°C to 40°C generated the sulfonated derivatives (**11**, R'=4-MeO- or 4-$EtOC_6H_4$), which were characterized as either the barium or S-benzylthiuronium salts. However, all attempts to isolate these compounds as the free acid *via* neutralization were unsuccessful and resulted in the isolation of the non-sulfonated sydnone **5** (R=H).

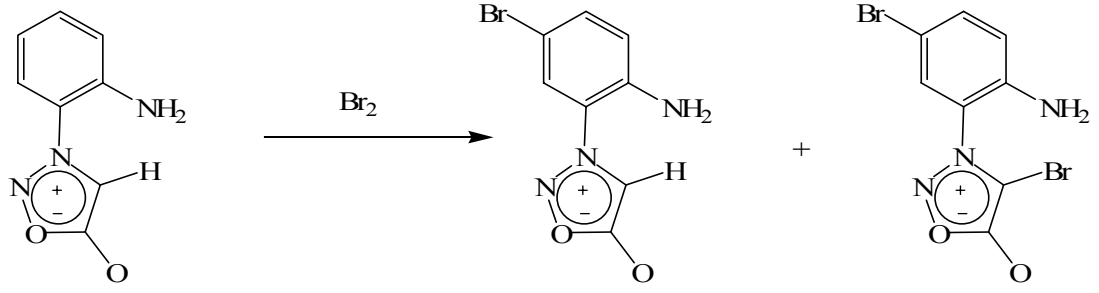


5, R = H **11**

C. Substitutions at the Aryl Ring of 3-Arylsydnones

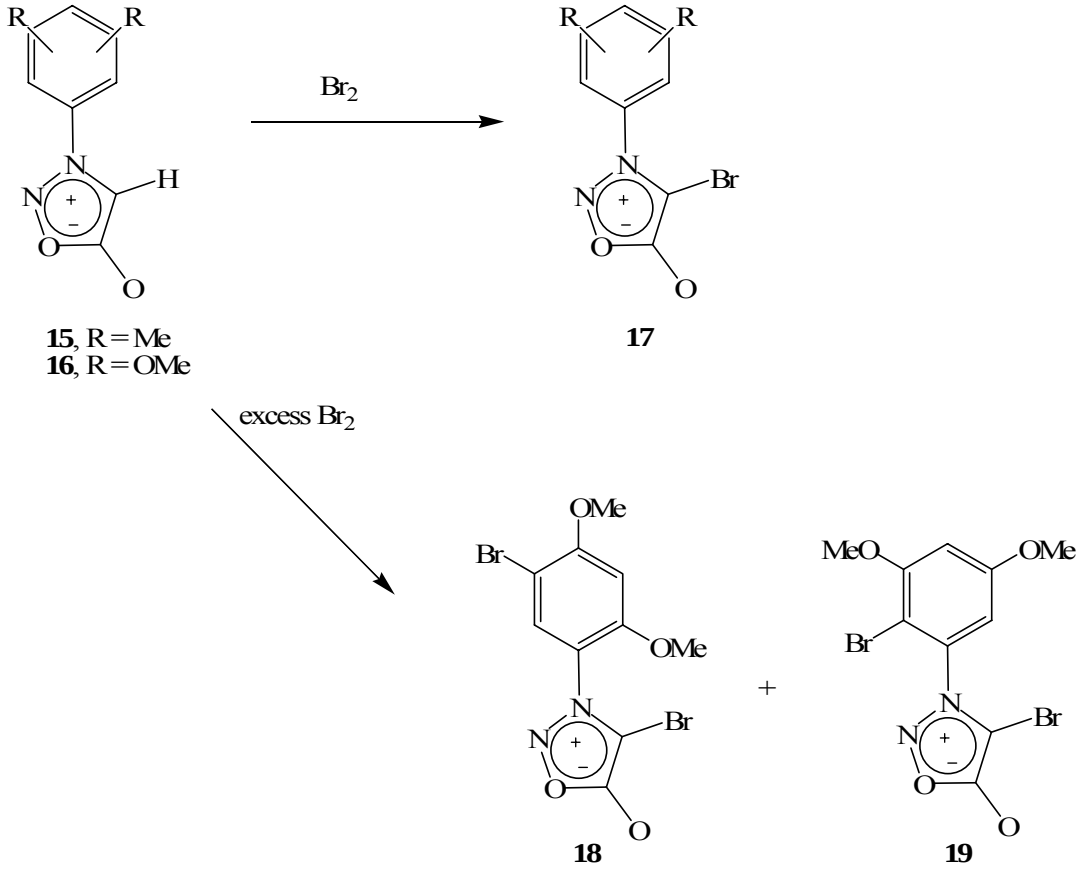
Generally, reaction of 3-arylsydnones with electrophiles occurs readily at the sydnone C-4 position due to the considerable partial negative charge residing at this position. The partial positive charge residing at the sydnone N-3 position apparently deactivates the juxtaposed aryl moiety.

To attempt to effect aryl substitution in preference to sydnone C-4 substitution, it was decided to generate a competitive situation for reaction with electrophiles by using an activated 3-aryl sydnone, *e.g.* 3-(2-aminophenyl)sydnone (**12**). It was reported that the major products obtained were derived from bromination on the aryl ring and are 3-(2-amino-5-bromophenyl)sydnone (**13**) and 3-(2-amino-5-bromophenyl)-4-bromosydnone (**14**). For the first time, it was demonstrated that the aryl moiety could compete with the sydnone ring for electrophilic substitution. On an interesting note, when NBS is added slowly to **12**, only **13** is formed in a 70% yield.[45]

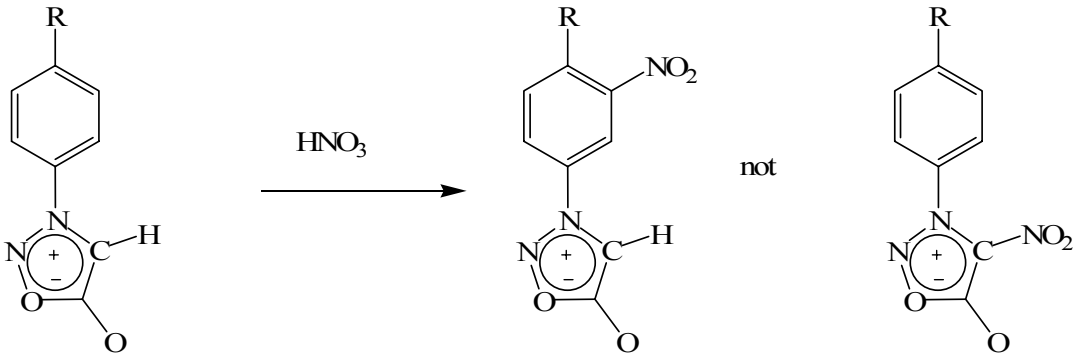


12 **13** 13% Yield **14** 25% Yield

Upon further examination of this methodology, it was shown that the bromination of a series of dimethylaryl- or dimethoxyarylsydnones (**15** and **16**, respectively) with 1 equivalent of bromine occurred at only the C-4 position of the sydnone ring (leading to **17**).[78] It was shown also that even when treated with excess bromine, only the most activated sydnones, the 3-(2,4- and 3,5-dimethoxyphenyl) derivatives, were brominated on the aryl ring, to give **18** and **19,** but only *after* bromination had occurred at the sydnone C-4 position.



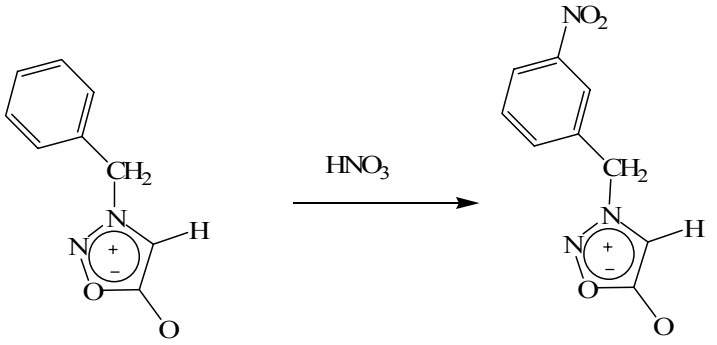
The nitration of an activated 3-arylsydnone preferentially occurs at the aryl moiety and not at the sydnone C-4 position. When exposed to nitrating conditions, activated aryl sydnones (*cf.* **20**) afford the products of nitration on the aryl ring **21** and not the anticipated 4-nitro derivatives **22**.[46]



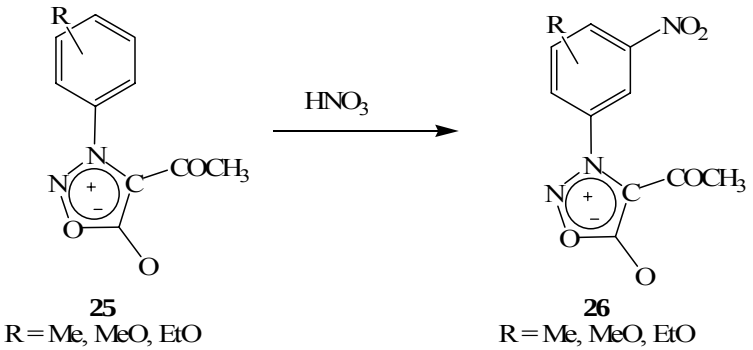
20 **21** **22**

R = Me, MeO

More recently, Tien and coworkers[40, 80] have shown that the *meta*-nitroaryl products **24** and **26** were obtained when either 3-benzylsydnone (**23**) or various 3-substituted-4-acetylsydnones **25** were treated under nitrating conditions. In the latter case, the acetyl group in the products **26** could be removed with barium hydroxide.



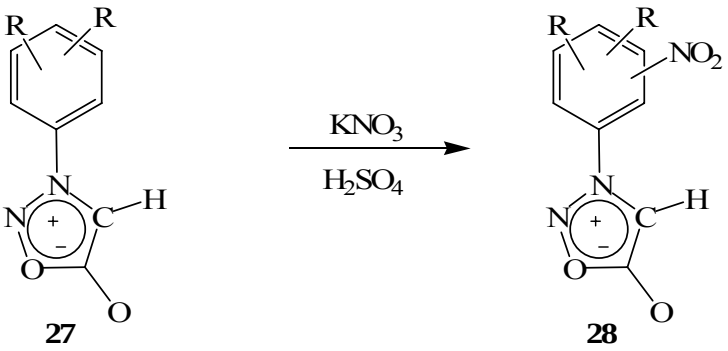
23 **24**



25
R = Me, MeO, EtO

26
R = Me, MeO, EtO

Turnbull, Blackburn, and Miller have examined nitration of 3-arylsydnones with multiple electron-donating groups (methyl groups) on the aryl ring.[81] Again, exclusive aryl ring nitration was observed, with a strong tendency for nitration *meta* to the sydnone ring. When nitration was forced to occur between two substituents on the aryl ring, it was shown that the favored position was between the sydnone ring and a methyl group, rather than between the two methyl groups.



27 **28**

a) R = 2,4-Me; b) R = 3,4-Me; c) R = 2,5-Me;
d) R = 2,3-Me; e) R = 2,6-Me; f) R = 2,4,6-Me

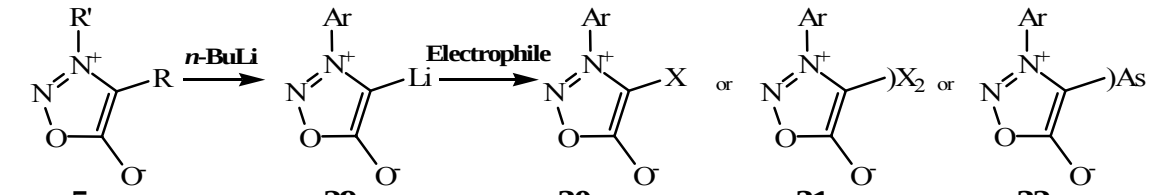
II. Metallation of Sydnones

A. Metallations exclusively at the 4-position

Metallation of sydnones, the most commonly studied substitution at the sydnone C-4 position, has yielded several interesting compounds including 4-lithio, 4-cupro, 4-chloromercurio, and 4-palladium (0)[82] or nickel (II)[83] complexes.

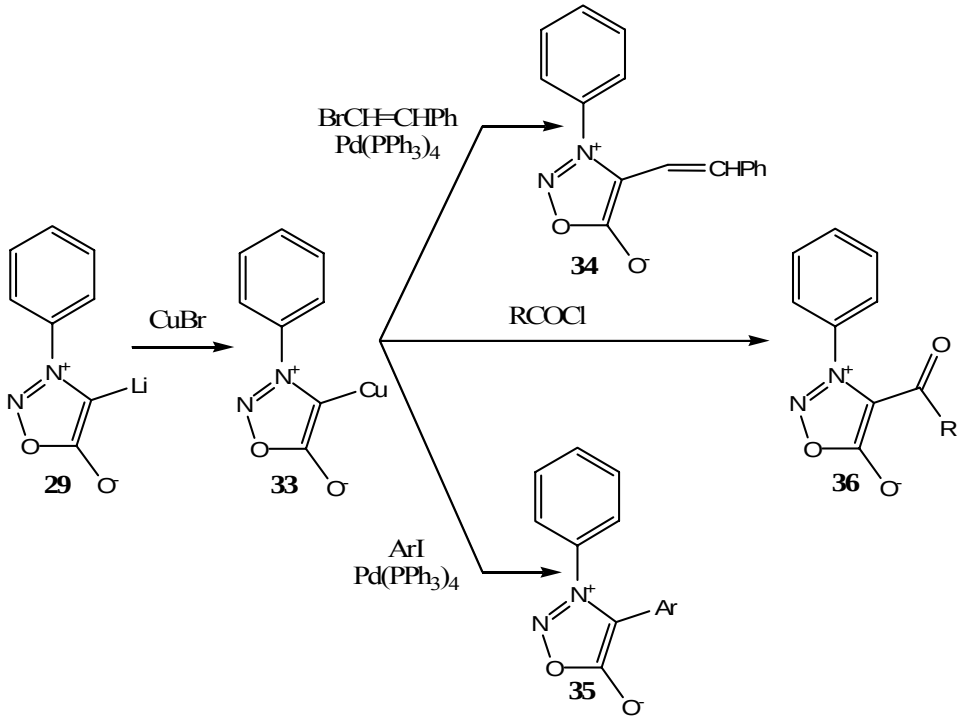
The most versatile of the above mentioned compounds have been the 4-lithio sydnones **29**. These compounds are generally prepared from 3-phenyl sydnone **5** (R = H, R' = Ph) or 4-bromo-3-phenylsydnone **5** (R = Br, R' = Ph). Reactions of either alkyl or aryl disulfides or diselenides with **29** gave the 4-sydnonylsulfides or 4-sydnonylselenides and their derivatives **30a**.[84] Additionally, the bissydnonyl sulfide and selenide **31** have been prepared in an analogous manner by treating **29** with the appropriate dicyano,

disulfide or diselenide.[84] Extending this methodology to arsenic trichloride and diphenylchlorophosphorane[84] resulted in the preparation of the corresponding sydnonylarsine **32** and phosphine **30b**, respectively. Recently, 4-carboxysydnones **30c** have been prepared by carboxylation of **29** with carbon dioxide.[85] Additionally, Tien and coworkers[75] have shown that various 3-substituted sydnones can be lithiated and exposed *in situ* to either N,N-dimethylformamide, N,N-dimethylacetamide, or acetaldehyde to afford the corresponding acylated **30d**, or hydroxylated **30e** derivatives.

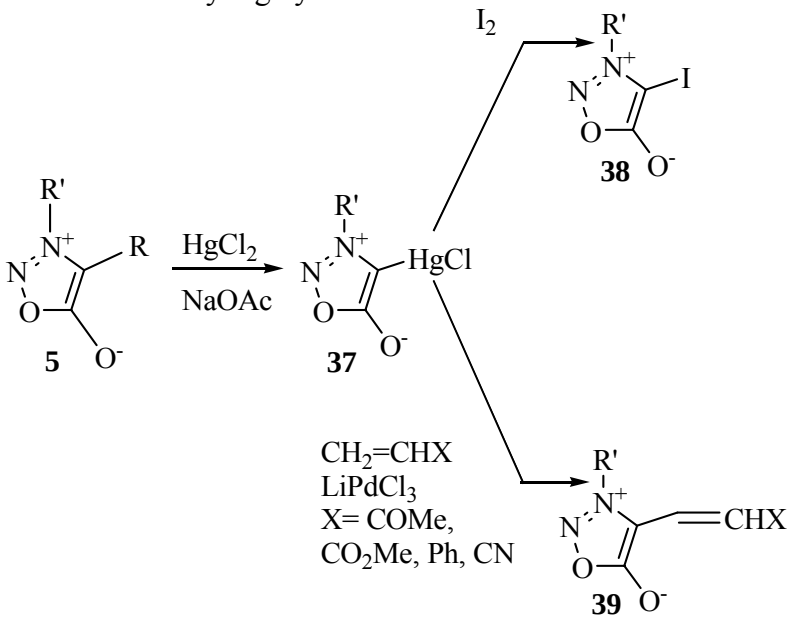


a: X = SR, S-C=S, Se
b: X = PPh_2
c: X = COOH
d: X = $COCH_3$, COH
e: X = $CH(OH)CH_3$

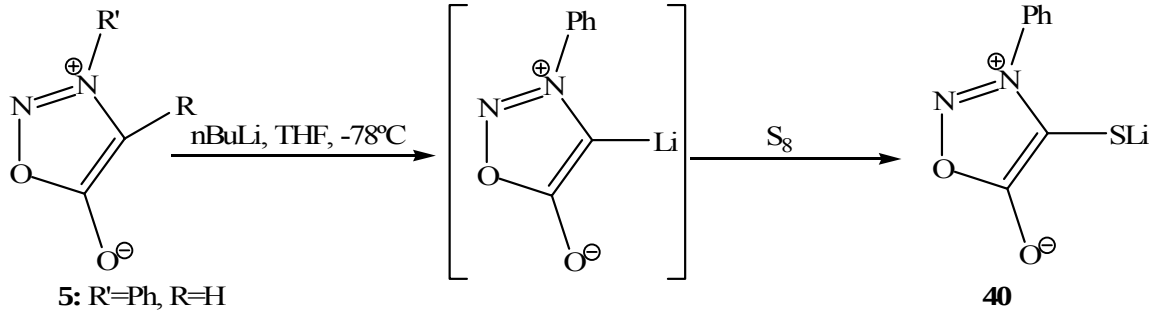
The reactivity of sydnone metal species can be modulated by changing the metal present at the 4-position. Thus, reaction of **29** with cupric bromide gives the stable copper species **33** which can be coupled to vinyl or aryl halides over a palladium (0) catalyst to yield 4-alkenyl **34** or 4-arylsydnones **35**.[86] Reactions of **33** with acid chlorides yield the corresponding 4-acyl sydnones **36**.[87] More recently, Kalinin and coworkers[88] have shown that sydnonyl cuprates **33** can undergo palladium catalyzed cross-coupling reactions with either heteroaryl iodides or alkynyl bromides to afford the corresponding 4-substituted sydnones in good to excellent yields.

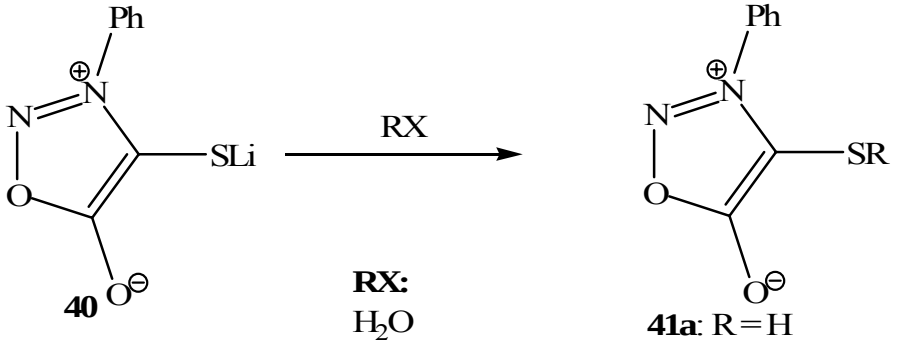


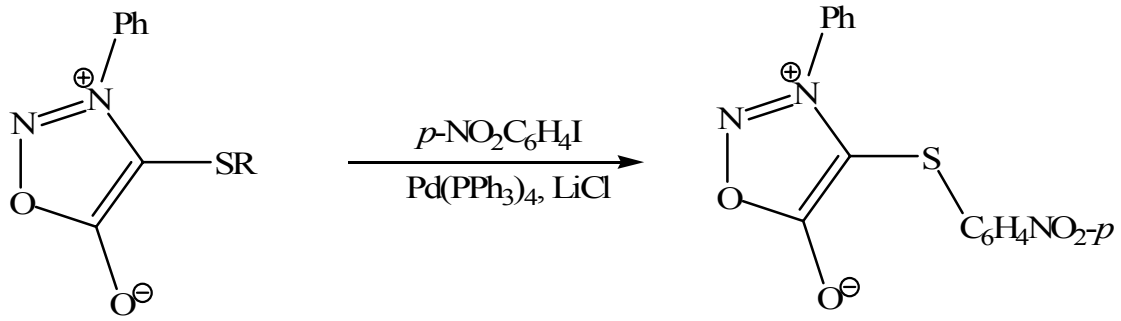
Reactions of 3-arylsydnones, **5** (R = H, R' = Ar) with mercuric chloride and sodium acetate in aqueous methanol at room temperature[89] yield the 4-chloromercurio species **37** which can be can then be treated with iodine to afford the 4-iodo derivatives **38**. More recently, Kalinin reported that reaction of the 4-chloromercurio intermediate with electron deficient olefins afforded only the *trans*-isomer of the corresponding 4-alkenyl product **39** in relatively high yields.[90]



Recently, Lebedev *et. al.*[91] investigated the introduction of alkyl- and arylthio substituents at the sydnone C-4 position by reacting 4-lithiosydnones with elemental sulfur. They discovered that reaction with elemental sulfur gave a lithium thiolate **40**. Further reactions upon **40** with water and a variety of organic halides gave the corresponding thiol and thioalkyl species **41a-d**, whereas a reaction with pivaloyl chloride afforded **41e**. It was also noted that reaction of **40** with Me_3SnCl yielded the corresponding tributyltin species **41f**. A Stille reaction of **41f** and *p*-iodonitobenzene yielded the sulfide **42**.





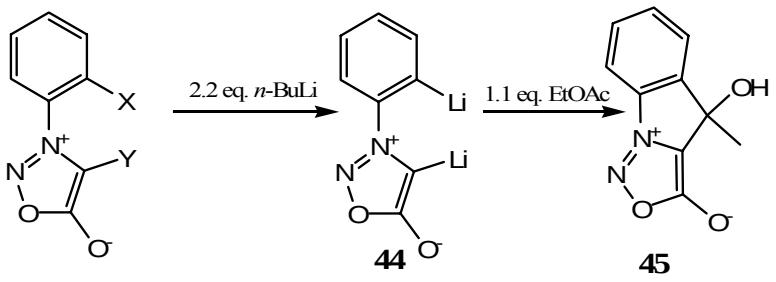


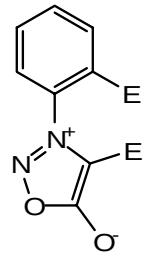
41f: R = Me_3Sn **42**

B. Dilithiations of 3-Arylsydnones

Dilithiation of 3-arylsydnones has become a recent focus of sydnone chemistry, and has been successfully achieved by Krein and Turnbull.[81, 92-94] Initially, a dilithio sydnone species **44** was made by the reaction of 3-(2-bromophenyl)-4-bromosydnone **43a** with butyllithium at -78 °C. Subsequent reaction with ethyl acetate afforded the known sydnoindole **45** in good yield. Krein and Turnbull applied this reaction to other esters, thus proving the reaction's versatility. An undesirable drawback, however, was the loss of weight going from starting material to product caused by the sacrifice of two bromine atoms. To limit this, 3-(2-bromophenyl)sydnone **43b** was used instead of **43a** under similar conditions, and it was found that the same transformations could be achieved. Upon further study, Krein and Turnbull found that the dilithio intermediate **44** could be prepared directly from 3-phenylsydnone **5** (R' = Ph, R = H) using N,N,N',N'-tetramethylenediamine (TMEDA) to increase the basicity of butyllithium and the *ortho*-directing effect of the sydnone ring, presumably after initial anion formation at the 4-position. Reaction of this dilithio species was undertaken with a variety of electrophiles to yield novel disubstituted sydnones (*cf.* **44** to **46-51**) and, more recently, the same

reaction has been found to be highly effective without the use of TMEDA by simply raising the reaction temperature from -78 °C to -50 °C.[95]

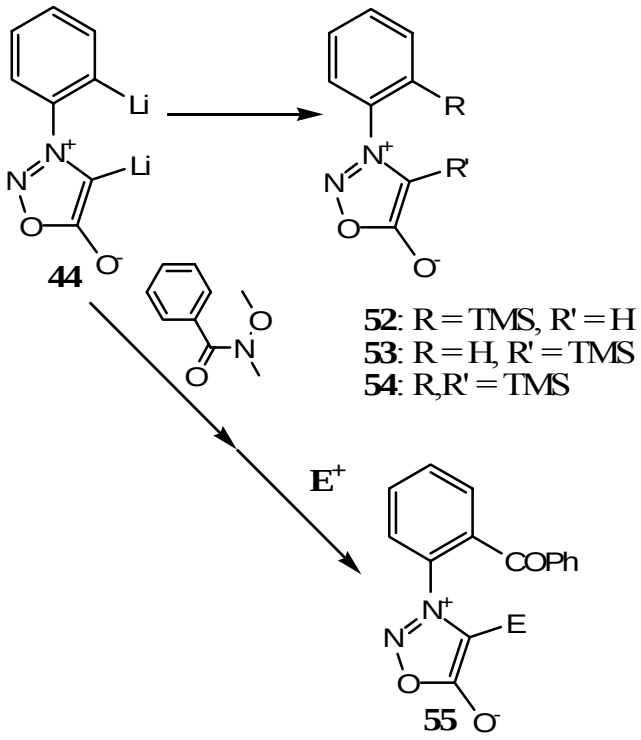




46: $E^+ = Br_2$, E = Br
47: $E^+ = HCON(CH_3)_2$, E = CHO
48: E^+ = PhCHO, E = CH(OH)Ph
49: $E^+ = I_2$, E = I
50: E^+ = PhSSPh, E = SPh
51: $E^+ = CH_3I$, $E = CH_3$

The pKa of the 4-sydnone proton is estimated to be 18-20 pKa units, while that of the *ortho*-aryl proton is estimated to have a pKa of approximately 40. Due the difference, Krein and Turnbull decided to explore the idea of selective substitution at the *ortho* site (after dianion formation). When the dilithio sydnone **44** was prepared and reacted with one equivalent of chlorotrimethylsilane, it was found to produce four products: *ortho*-substituted, sydnone C-4-substituted, disubstituted and unsubstituted **52-54**, **43b**, respectively. These results suggested that chlorotrimethylsilane was too strong an electrophile. Accordingly, Turnbull and Krein attempted reaction with a less reactive electrophile, and Weinreb's amides were chosen since they have known advantages in similar transformations. Thus, reaction of **44** with N-methoxy-N-methylbenzamide

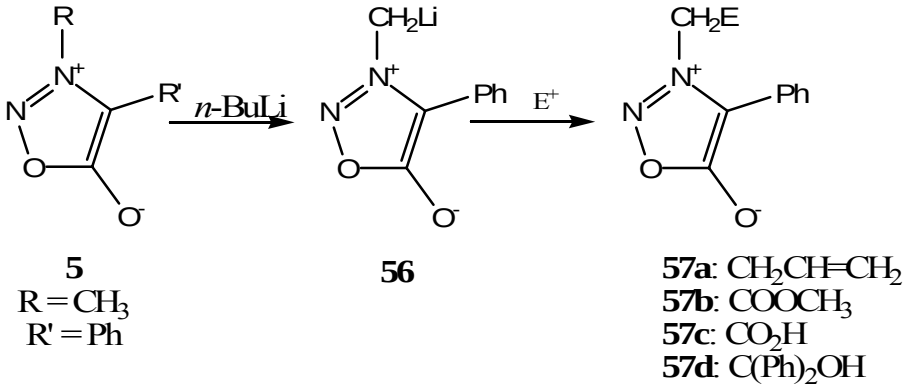
afforded the *ortho*-benzoyl species **55** (E = H) in good yield, and this process was extended to the preparation of other *ortho*-acylsydnones.[81, 92-94] Overall, this approach provided a "one-pot" synthesis of *ortho*-acyl sydnones from easily prepared 3-phenylsydnone. Since, after initial reaction at the *ortho*-aryl position, the sydnone anion remains, one equivalent of a second electrophile can be added to promote further functionalization at the C-4 position of the sydnone ring. This provides a route to many unsymmetrically functionalized sydnone species such as **55** (E = Br, TMS, *etc*.).



C. Miscellaneous Metalations

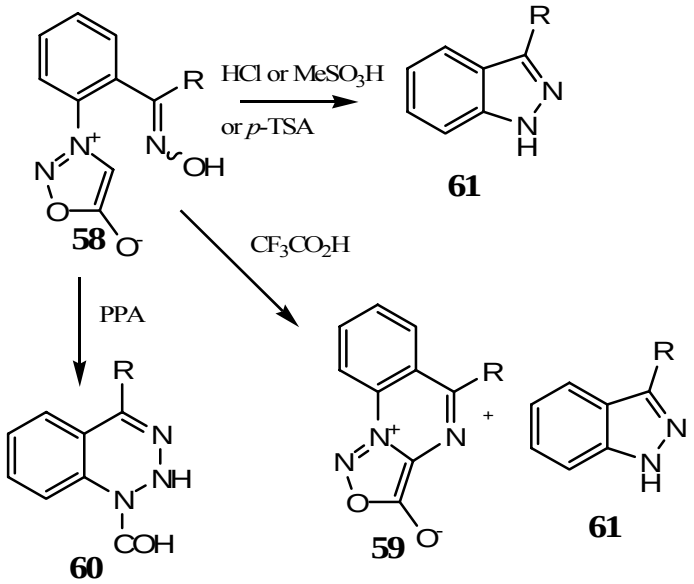
Kalinin and Cherepanov have explored metallation of 3-methyl-4-phenylsydnone **5** (R = Ph, R' = CH_3).[96] In their work, it was found that a proton could be abstracted from the methyl group of 3-methyl-4-phenylsydnone with butyllithium at -90 ºC, forming the rather unstable lithio intermediate **56**. Further reactions with a variety of electrophiles led

to several functionalized sydnones **57** (12% to 70% yields) through a common intermediate.

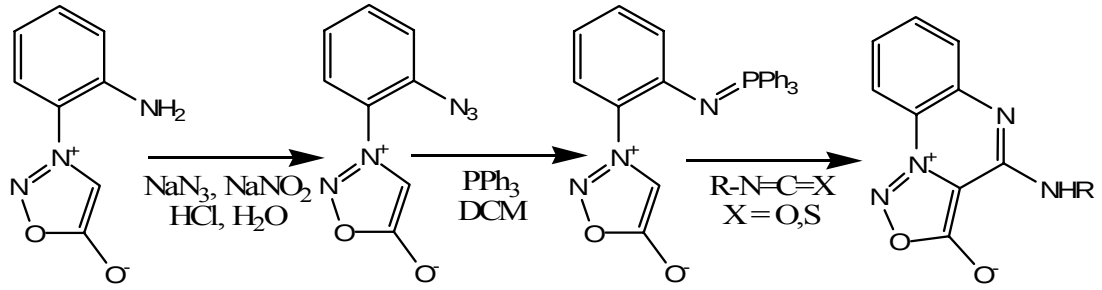


III. Reactions of *ortho*-Substituted Aryl Sydnones

Turnbull and Saljoughian reported [97] that by treating oximinosydnones **58** (R = Me or Et) with any one of a variety of acids, it was possible to obtain the corresponding sydnoquinazoline **59**, benzotriazine **60**, or indazole **61**, depending on which acid was used.



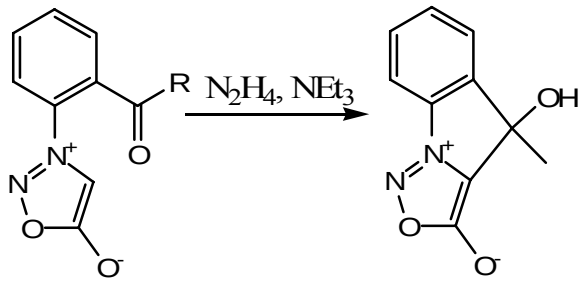
Additional fused-ring sydnone compounds, *viz*. 4-(arylamino)sydno[3,4-*a*]quinoxalines **62**, have been prepared in good to excellent yields (60-90%) by aza-Wittig carbodiimide formation followed by intramolecular electrophilic cyclization.[98]



12

62
R = Ph, 4-MePh, 4-MeOPh, 4- NO_2Ph

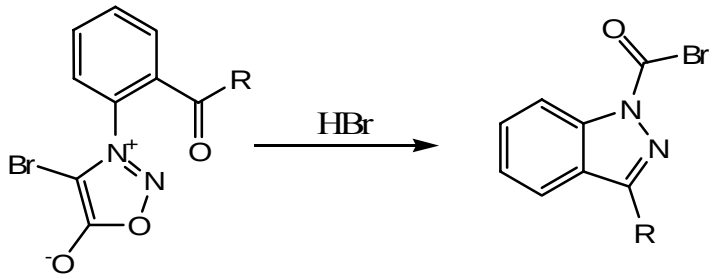
Two serendipitous discoveries have resulted in the preparation of the fused-ring sydnoindole **45** and various bromocarbonyl indazoles **64**. It was found that by treating 3-(2-acetylphenyl)sydnone (**9**, R = Me) with hydrazine hydrate under basic conditions, the major isolable product was the fused-ring sydnoindole **45** and not the anticipated hydrazone derivative.[99]



9 R = Me **45**

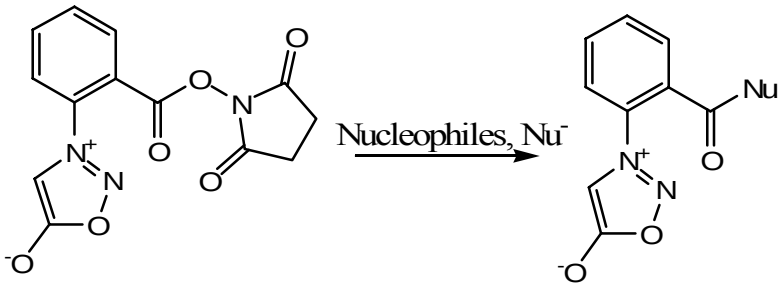
In an attempt to further extend this work, it was considered of interest to place a bromo-leaving group on the methyl side-chain. Accordingly, 3-(2-acetylphenyl)-4-bromosydnone, **63** (R = Me) was treated with Br_2/hν or $CuBr_2$. Surprisingly, the

bromocarbonylindazole **64** (R = Me) was obtained rather than the expected sydnone **63**, R = CH_2Br. It was speculated that the transformation was a result of the formation of HBr *in situ*, and, to test this, a variety of 4-bromo *ortho*-acyl sydnones *cf.* **63** were subjected to a stream of HBr gas; indeed the corresponding bromocarbonylindazoles **64** were formed in good yield (60-85%).[100]



63 **64**

One hindrance to the study of the reactions shown above has been that sydnones with an *ortho* carbonyl substitution are relatively hard to come by; they often must be made in several steps starting from the appropriate aniline derivative. In addition to the work done by Turnbull and Krein using the Weinreb's amides, recent work has shown that a variety of *ortho*-acylarylsydnones can be prepared from one or two intermediates by reacting nucleophiles with activated *ortho* carbonyl species.[101] As an example, 3-[2-(N-succinimido)oxycarbonyl)phenyl]sydnone (**65**) was reacted with twelve different nucleophiles to afford the corresponding *ortho*-acylarylsydnones **66** in yields ranging from 23% to 63%.



65 **66**

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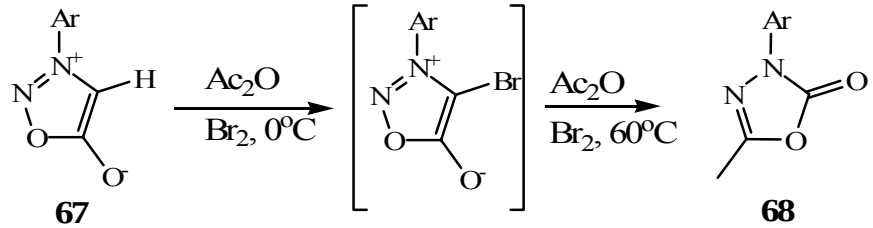
IV. Miscellaneous Reactions of Sydnones

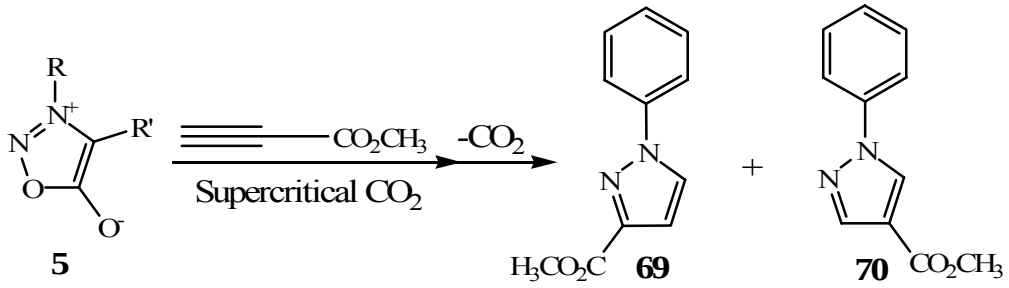
Mallur, Bharati, and Badami used sydnones as intermediates to 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones[59] with the objective of testing the latter for antimicrobial activity. The desired 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones **68** were prepared from 3-arylsydnones **67** by reaction with bromine in acetic anhydride, as is illustrated with a general example, below. The transformation is useful and, overall, twenty different oxadiazolinones were prepared in yields of 70-90%, most of which showed anti-bacterial and anti-fungal activity.



67 **68**

In their report, the suggested mechanism involves initial sydnone bromination to form a 4-bromo intermediate that is not isolated, followed, at increased temperature, by a 1,3-dipolar cycloaddition between the 4-bromosydnone and acetic anhydride. Since no attempt was made to remove HBr formed as a by-product and the unprecedented nature of the suggested cycloaddition, this mechanism seems suspect.

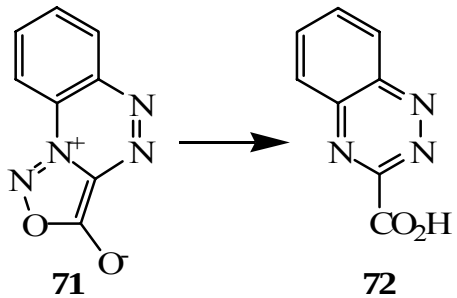
Further work concerning the ability of a sydnone to participate in 1,3 cycloadditions was carried out by Turnbull, McGowin and Totoe. This work involved a known sydnone reaction, *viz*. the reaction of 3-phenylsydnone, **5** (R = H, R' = Ph) with methyl propiolate, under slightly different conditions, namely using supercritical carbon dioxide as a solvent in place of toluene.[102]



In this reaction, two products were isolated. These two regioisomers (**69** and **70**) formed due to methyl propiolate being unsymmetrical. The temperature in the supercritical fluid reactor was varied, as well as the pressure, to see if this had an effect on reaction selectivity. In summary, it was found that increasing reaction temperature decreased selectivity while increasing reaction pressure increased selectivity. This showed that reaction in supercritical carbon dioxide provided a selectivity advantage over running the reaction under the standard conditions (toluene, heat). Further, it was shown that the reaction could take place in a "green" solvent (carbon dioxide versus toluene).

Aims of Present Research

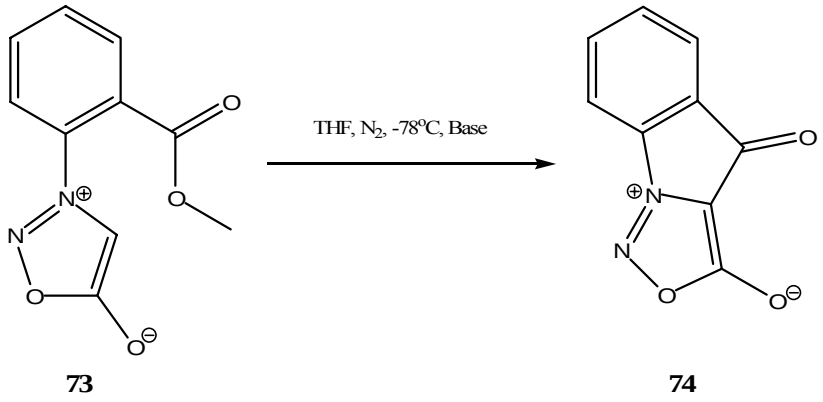
The primary goal of this current research was to provide efficient avenues to the sydnoindolone **74** and to study the chemical and physical properties of this species, with the hope that this novel sydnone, or a derived product, would act as a nitric oxide (NO) prodrug. Work done by Turnbull and Preston[102] had shown previously that the sydnobenzotriazine **71**, a fused-ring sydnone, cleaved hydrolytically to yield the benzotriazine carboxylic acid **72** (Figure 1). It appeared likely that the undetected other product in this process was NO (or a related species) and, accordingly, it was of interest to prepare analogous species. In this work, it was elected to explore whether or not a fused-ring sydnone with a five-membered ring system, rather than the six-membered ring system in the sydnobenzotriazine, would allow for a similar cleavage and potential release of nitric oxide. Previous work has not provided successful avenues to fused-ring sydnones with an sp^2-hybridized bridge and, accordingly, it was recognized that this could present a problem with the successful formation of such a species (as in **74**), as well as the potential instability of such a compound.



71 **72**

Figure 1: Conversion of sydnobenzotriazine **71** to benzotriazine **72** as observed by Turnbull [102].

The projected synthetic route, as shown in Scheme 1, anticipated that the target sydnoindolone could be synthesized from the 3-(2-methoxycarbonylphenyl)sydnone (**73**) starting material *via* a lithiation protocol involving abstraction of the proton at the sydnone ring 4-position, followed by an intramolecular attack of the resulting anion at the ester. Due to the nature of the starting sydnone and the potential susceptibility of the ester moiety to nucleophiles, it was expected that the base used would have to be non-nucleophilic (*e.g*. LDA or LHMDS) to enhance the likelihood that the fused ring sydnoindole **74** would be formed.



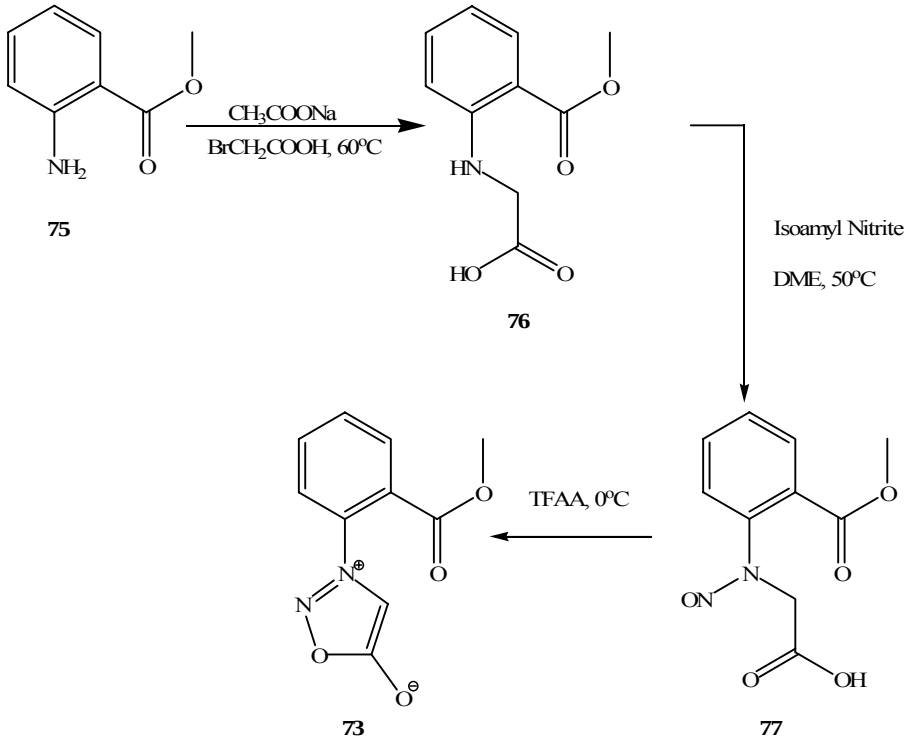
73 **74**

Scheme 1: Projected synthesis of the target sydnoindolone.

It was anticipated that, upon successful, initial formation of the sydnoindolone **74**, modification and optimization to obtain the target sydnoindolone **74** in greater yields would be studied. With optimization reached, further reactions (*e.g*. with Wittig or Grignard reagents) would be carried out to test the reactivity of the target sydnoindolone **74** and to form other interesting, new sydnone species. The sydnoindolone, as well as the subsequently formed sydnones, would then be studied further to determine what conditions (if any exist) would allow for the breakdown of the sydnone ring to release nitric oxide.

Discussion

With the aims of the research set, the initial step was to make the starting material, 3-(2-methoxycarbonylphenyl)sydnone (**73**). This compound had been made previously[104], so it was elected to use the described method of reacting methyl anthranilate **75** with sodium acetate and bromoacetic acid in water to yield the corresponding glycine **76**. The glycine then undergoes nitrosation with isoamyl nitrite in dimethoxyethane, followed by cyclization with trifluoroacetic acid (TFAA) in dichloromethane to yield the sydnone starting material (Scheme 2). In the present work, the sydnone product was purified and identified as the desired starting material by comparison (TLC, IR, m.p.) with known samples previously made in our research lab. The overall yield of the reaction ranged from 33-44% with the biggest loss of material coming from the formation of the corresponding glycine (~40-50%).

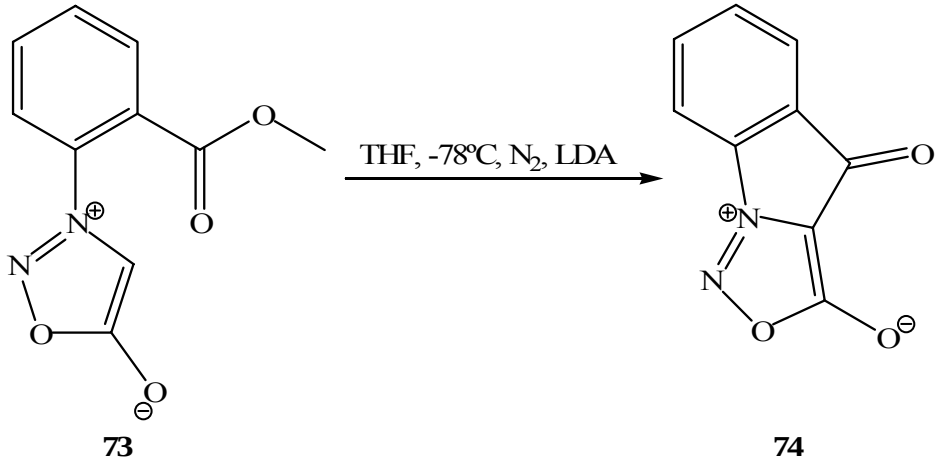


Scheme 2: Formation of the sydnone starting material **73**.

It was elected to try to optimize the reaction in an attempt to improve the yield of the starting material. Since the greatest loss appeared to be within the formation of the glycine **76**, this step was the obvious choice for improvement. In recent work done in our research lab[105], it had been shown that, for a similar transformation, increasing the amount of water for the reaction led to an increase in the yield of the glycine. This methodology was applied to the present reaction as well, but results from this modification proved to be of little benefit, as similar yields were obtained.

The next step in the research was to then form the target sydnoindolone **74**. It was elected to attempt this using lithiation techniques developed in our lab to abstract the sydnone C-4 position using an organolithium base in a relatively small excess (See Scheme 3). This one-step approach seemed like a possible route to the target sydnoindolone **74**, but some concern was raised as to the stability of such a compound since there was no indication of previously made sydnones with the sp^2 hybridized bridge. It was elected to use a base that was known to be non-nucleophilic to avoid a potential reaction with the carbonyl of the phenyl ring ester. Lithium diisopropylamide (LDA) was used since it is strong enough to abstract the proton needed (sydnone C-4, pKa ~ 20) and does not typically display nucleophilic tendencies. The starting sydnone **73** was dissolved in tetrahydrofuran (THF, 40mL), the mixture cooled to -78ºC and the reaction run under anhydrous conditions in a nitrogen atmosphere for 1 hour with monitoring by TLC (Scheme 3). It was noticed during this time that the starting material was no longer present, leading to the conclusion that reaction was complete. Isolation of the target sydnoindolone **74**, however, proved to be difficult as a large mixture of products resulted and identification of the target molecule within the mixture appeared to

be futile. It was conjectured that this complex reaction might be due to intermolecular reactions caused by the high concentration of the system. Accordingly, it was decided to increase the amount of THF in the reaction to lower the concentration in hopes of preventing possible intermolecular reactions. Unfortunately, even after several attempts using different concentrations, the reaction with this modification provided a similar mixture of products to the situation initially. These results led to the belief that the sydnoindolone **74**, if it was being formed, was unstable due to the C=O bridge and that isolation of this product would not be possible. However, it was still decided to use the increased amount of THF (*viz.* 100mL) for future reactions to minimize the possibility of intermolecular reactions.

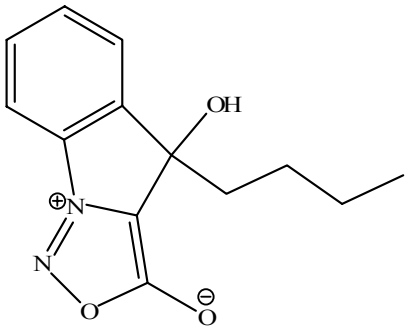


73 **74**

Scheme 3: Attempted formation of the sydnoindolone **74** from 3-(2-methoxycarbonylphenyl)sydnone (**73**) using LDA

From the reaction mixtures described above, there was no identification made on whether the sydnoindolone target **74** was indeed being generated from this reaction. It seemed likely that, if the sydnoindolone was indeed an intermediate, "trapping" of it *via* the addition of a nucleophile into the reaction should lead to interesting products, the isolation of which would point to the intermediacy of **74**. For this research, it was

decided first to use other organolithium species as the "trapping" nucleophiles to yield the corresponding sydnoindoles, compounds that had been generated previously within our lab. To effect this possibility, the LDA was added to a solution of the starting sydnone **73** in THF at -78°C and allowed to react for one hour. After this time, 1.5 equivalents of n-butyllithium were added and allowed to react for approximately 1 hour to yield the 5-hydroxy-5-butylsydno[3,4-*a*]indole (**78**) in a 10 % yield. This new sydnoindole species was compared to previously made sydnoindoles[92] and was shown to be identical by TLC, IR and NMR data. The IR spectrum of the new compound showed a strong peak near 3350 cm^{-1} (3352 cm^{-1}) for the alcohol stretch of the sydnoindole as well as a strong peak near 1730 cm^{-1} (1740 cm^{-1}) for the sydnone C=O stretch. Also, the carbon NMR showed the sydnone C-5 position to be near 162 ppm and the bridging carbon with the attached alcohol at 76 ppm, correlating to previously generated sydnoindoles. To further test the value of this "trapping" process, another organolithium base, methyllithium, was used in the same manner to yield the known 5-hydroxy-5-methylsydno[3,4-*a*]indole (**45**) in a 33 % yield. The latter was also shown to be identical to a known sample *via* TLC, IR, and NMR spectroscopy.



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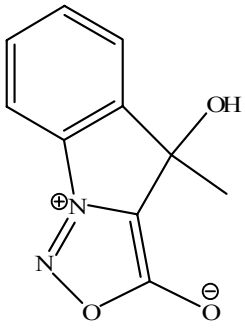
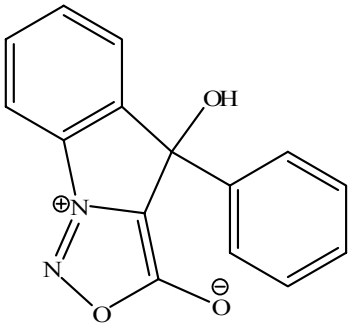


45

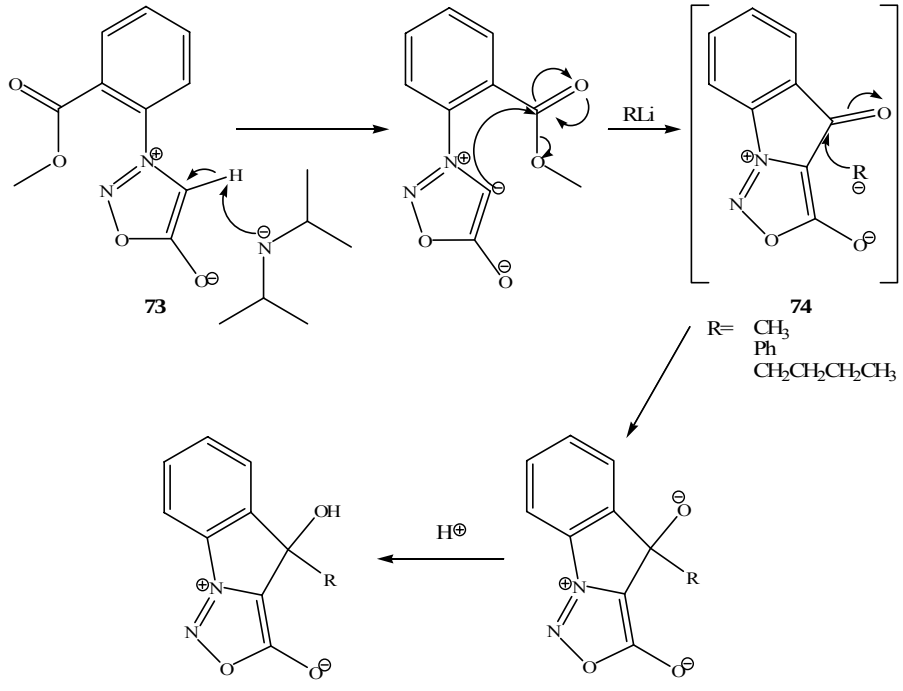


79

With these results in hand, it was imperative to see whether these yields could be improved. The methyl indole was chosen for this test as it had already been previously

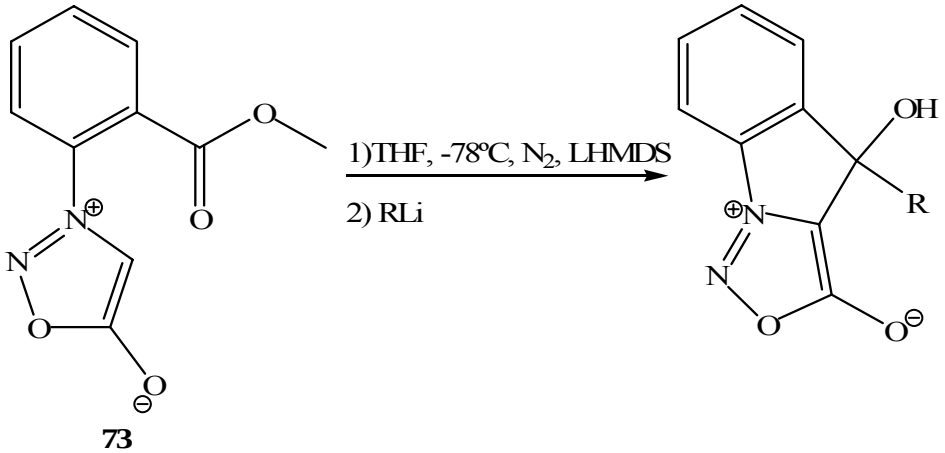
generated in our research lab. The two factors from the second step determined to be those most amenable to modification were the number of equivalents of the second base employed and the reaction time after addition of the second base / nucleophile. Accordingly, the reaction was altered to the use of 1.5 equivalents of the second base / nucleophile, and a reaction time of 2 hours. In addition, two other reactions were attempted increasing the amount of the second base / nucleophile up to 2 and 3 equivalents, while maintaining the original reaction time of approximately one hour. Unfortunately, in all of these cases the yields obtained were similar to those obtained before the modifications, *viz*. 20%-25%, and, accordingly, it was concluded that the initial condition of 1.5 equivalents for one hour would be used for future reactions involving sydnoindole formation. Even given this conclusion, it was envisaged that there would still be potential for improvement from examination of the first step of the reaction, *viz*. the addition of LDA. Thus, test reactions were run where the presence of the sydnone starting material in the reaction mixture was monitored carefully so as to eliminate as many of the side products as possible. In this regard, by TLC monitoring, it was determined that the starting material had fully reacted with the LDA after approximately ten minutes, rather than having to allow the reaction to run for 1 hour. Upon addition of the determined amount of methyllithium and the newly determined reaction time, workup and isolation yielded the target 5-hydroxy-5-methylsydno[3,4-*a*]indole (**45**) in a 44% yield. Another test run on this protocol involved the use of phenyllithium as the second base / nucleophile to form the corresponding 5-hydroxy-5-phenylsydno[3,4-*a*]indole (**79**), which had also been generated previously within our lab. Using the newly developed methodology, the target 5-hydroxy-5-phenylsydno[3,4-

a]indole (**79**) [characterized by comparison (TLC, IR) with an authentic sample] was generated in a 25% yield. The considerable drop in yield is hard to explain but may be due to the lower reactivity of the phenyllithium, compared to methyllithium. The proposed mechanism for these reactions is shown in Scheme 4. Although it is certainly possible that these products result from a different mechanistic process, the complete loss of starting material, as indicated by TLC evidence, suggests that the proposed mechanism is correct. In this regard, if only the proton attached to the sydnone C-4 position had been abstracted and the fused-ring sydnoindolone **74** was not formed as an intermediate, the reaction would have shown starting material present by TLC since the anion at the sydnone C-4 position would have been protonated on work-up to afford **73**.



Scheme 4: Proposed mechanism of action involving the use of LDA and a subsequent organolithium base to obtain the desired sydnoindole species.

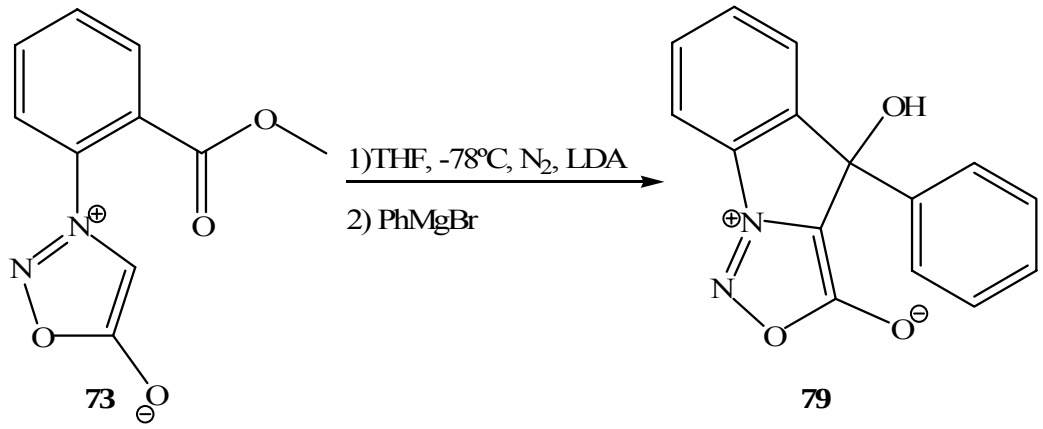
While the optimization attempts thus far had improved the process leading to the fused indole species **45**, presumably *via* the sydnoindolone **74**, there was still a good amount of room for further improvement. In this regard, to this point, no attempt had been made to alter the base used initially to abstract the sydnone C-4 proton and, accordingly, instead of using LDA, it was decided to attempt this reaction with lithium hexamethyldisilylamide (LHMDS). The latter is a more hindered, less reactive base than the previously used LDA and, accordingly, it was envisaged that, if any of the by-products were due to intermolecular reactions with LDA these would be minimized by the use of LHMDS. Due to this base's extra steric hindrance, the initial, proton-abstraction step was given a slightly longer time to take place before the addition of the second organolithium base / nucleophile. Upon addition of the second base, the target sydnoindoles **45**, **78**, and **79** were generated using the same conditions previously established (Scheme 5). However, a significant drawback was that the yields for these reactions came out much lower than those from the previous method. Accordingly, while this is another means to generate the desired sydnoindoles due to this limitation it does not appear to be a practical alternative process.



73

Scheme 5: Reaction to form sydnoindoles using LHMDS

It was conjectured that another avenue to these sydnoindoles would be to use a Grignard reagent as the nucleophile. This again follows the premise that the target sydnoindolone **74** is being generated since, in order for the Grignard reaction to take place, a carbonyl group would have to be present at some point during the reaction. The first nucleophile chosen was phenylmagnesium bromide (Scheme 6). This particular reagent was chosen due to its availability within our lab and the ability to test the product against the previously made sydnoindole **79**. When the reaction was attempted with the sydnone ester **73**, employing the procedure as optimized previously, but with the variation that PhMgBr was used instead of PhLi, the reaction resulted in the formation of the corresponding sydnoindole **79** in a yield (23%) comparable to that obtained previously with phenyl lithium (25%).

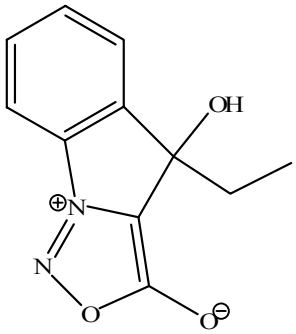


Scheme 6: Grignard reaction of the sydnone starting material **73** to form 5-hydroxy-5-phenylsydno[3,4-*a*]indole (**79**).

This positive result suggested that other sydnoindoles could be generated using this reaction method and, accordingly, two other Grignard reagents were explored, *viz*. ethylmagnesium bromide and vinylmagnesium bromide. Again, both of these were

chosen due to their availability within our lab and the fact that the ethylmagnesium bromide would generate a 5-hydroxy-5-ethylsydno[3,4-*a*]indole (**80**) that had been previously generated within our lab. It was anticipated that the vinylmagnesium bromide would yield 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**) similar to that from ethylmagnesium bromide, but with the difference that a vinyl group would be present that could provide another location within the molecule for subsequent reactions. In addition, if the latter reaction were successful, then the resulting sydnoindole would be of a different type from any previously made in our lab, since vinyllithium was not available commercially but vinyl magnesium bromide was. The results of the reactions of these Grignard reagents as the second nucleophile (as outlined previously) were somewhat promising as both the target indole from the ethylmagnesium bromide [5-hydroxy-5-ethylsydno[3,4-*a*]indole **(80)**] and that from the vinylmagnesium bromide [5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**)] were generated in yields of ~15%. The product from the ethylmagnesium bromide was identical to the authentic sydnoindole **80** *via* TLC, IR, NMR and m.p. examination and the new sydnoindole **81** was analyzed with TLC, IR, m.p., ^{1}H and ^{13}C NMR. The IR showed a strong peak at 3344 cm^{-1} for the alcohol O-H stretch and the strong sydnone C=O stretch at 1736 cm^{-1}. The ^{1}H NMR showed the alcohol hydrogen at 6.67 ppm, a doublet of doublets for the CH near 6.12 ppm and the two distinct, vinyl hydrogens from the CH_2 as 2 doublets at 5.59 ppm and 5.53 ppm for one and 5.32 ppm and 5.28 ppm for the other. The distinct difference is due to the proximity of the hydrogens in relation to the alcohol on the bridging carbon, as the first one stated is closer to the alcohol than the latter. As with previously synthesized sydnoindoles, the ^{13}C NMR showed the sydnone C=O near 160 ppm (162.9 ppm) and the

bridging carbon in the range of 70-80 ppm (75.38). The sydnone C-4 position was shown at 110.2 ppm compared to the starting sydnone's (**73**) C-4 position at 97.8 ppm. The –CH_2 from the attached vinyl group appears on the spectrum at 116.0 ppm and the –CH appears at 135.0 ppm. Although the yield for the sydnoindole **81** was low, this was a new compound and it was anticipated that further work on the process leading to its preparation would be likely to improve the yield.



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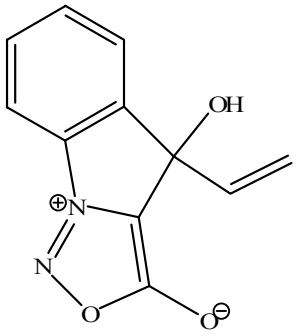
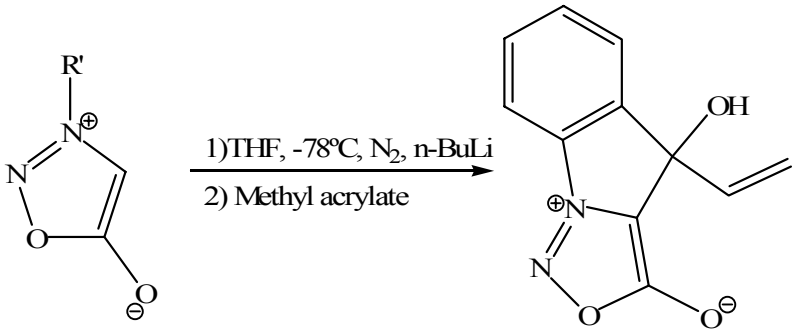


81

With the discovery of the 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**), a more efficient method for the synthesis was explored. It was conjectured that, by taking 3-phenylsydnone (**5**, R=H, R'=Ph) and methyl acrylate and reacting them under the dilithiation conditions previously mentioned, the vinyl sydnoindole **81** would result directly (Scheme 7). The reaction was run successfully with the target being synthesized in a 14% yield. Although the percent yield is comparable to that from the Grignard reaction previously described, the use of 3-phenylsydnone is more efficient since it can be made in 2 steps from commercially available N-phenylglycine whereas the preparative route to sydnone ester **73** involves a low yield, 3 step protocol.

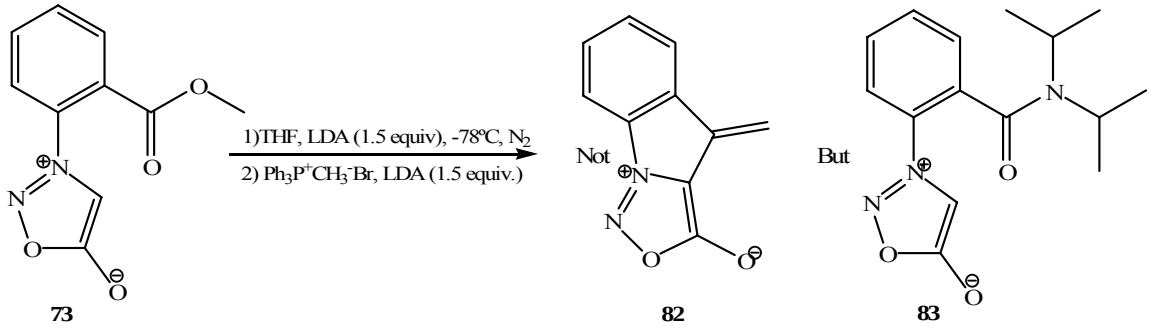


5 R=H, R'=Ph **81**

Scheme 7: Formation of 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**) from 3-phenylsydnone **5** (R' = Ph, R = H)

With the expectation that the sydnoindolone **74** was being formed, it was decided to attempt a Wittig reaction. This reaction involved the use of methyltriphenylphosphonium bromide and excess quantities of base, again LDA, to generate the nucleophilic ylide, which it was anticipated would react with the ketone moiety in the sydnoindolone **74** to form a fused-ring sydnone alkene **82** (see Figure 2). Thus, the starting sydnone **73** was dissolved in 100mL of THF and cooled to -78ºC, at which time 1.5 equivalents of LDA were added and allowed to react for the previously determined amount of time. Then the Wittig precursor was added (1.1 equiv.) and more LDA (1.5 equiv.) was provided to generate the ylide. Knowing that a Wittig reaction with a ketone is often a very slow process, the reaction was allowed to run for approximately 4 hours with monitoring by TLC to confirm product formation. Isolation of a compound from the complex reaction mixture showed promise of formation of the target compound **82**, since the initial IR data were in line with those expected for the desired molecule. Although the presence of a peak near where the sydnone C-4 position would normally show (~3150-3100 cm^{-1}) was surprising, the C-H stretch of the alkene

formed could also account for this peak. To aid in the identification of this compound, ^{1}H NMR spectroscopy was used. The spectrum from the ^{1}H NMR showed different results from those expected for **82** as there appeared to be two distinct multiplets in the range of 3.4-6.7 ppm as well as two distinct doublets of doublets from 1.00-1.13 ppm and 1.41-1.53 ppm. The multiplets, combined, integrated for a total of two hydrogens and the doublets of doublets integrated for approximately six hydrogens. Also the spectrum indicated that the sydnone C-4 position was not substituted and the sydnone C-4 hydrogen was present at 6.689 ppm. This suggested that the compound isolated had the structure **83** wherein the LDA had apparently acted as a nucleophile, possibly directly with the starting ester **73** (though, formation of the sydnoindolone **74** and reaction of the LDA with that intermediate, cannot be ruled out). As a test, another reaction was run using the same number of equivalents of LDA but without the presence of the methyltriphenylphosphonium bromide and allowing the reaction to run for the four hour period as before. TLC evidence showed that the product **83** was being formed. Strangely, this particular product was not seen in previous reactions, which may potentially be due to the large excess of LDA used as well as the greater length of time the LDA was allowed to react for this particular reaction. Due to time constraints, the very low yield and no particular interest in the newly formed compound, no further studies were undertaken on this particular reaction or its product.



73 **82** **83**

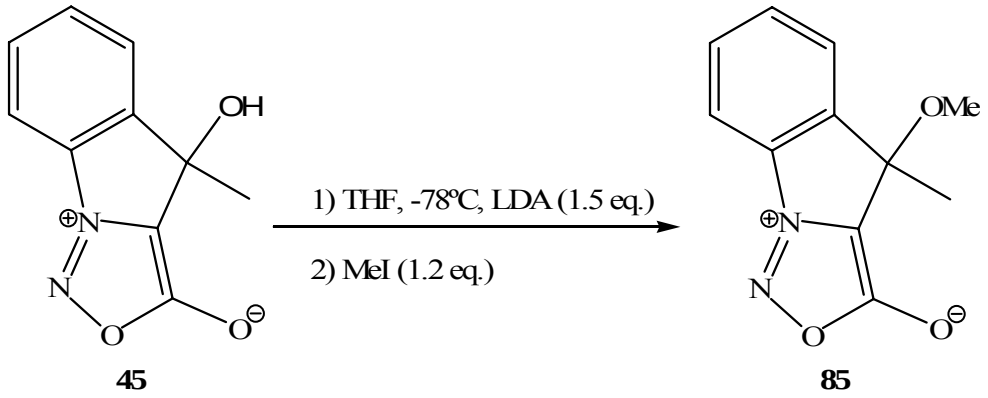
Figure 2: Attempted Wittig reaction

With some limited reactivity data for the target sydnoindolone in hand, it was decided to explore the reactions (if any) of the further derived sydnoindoles. Looking at the sydnoindoles obtained, it was decided to see if it was possible to substitute for the alcohol functionality in the sydnoindole. The sydnoindole used initially for all of these reactions was 5-hydroxy-5-methylsydno[3,4-*a*]indole **45** due to the greater yields of this compound produced from methods previously described in our lab., especially a very recent modification developed by G. Storer.[105] Expanding on what had already been described, Storer used 3-(2-acetylphenyl)sydnone **84** and LDA under dilute conditions (*viz.* 100mL THF) and was able to obtain the desired methyl sydnoindole species **45** in a yield of 66%.

84 **45**

Scheme 8: Intermolecular reaction of 3-(2-acetylphenyl)sydnone **84** with LDA to form 5-hydroxy-5-methylsydno[3,4-*a*]indole **45**.[105]

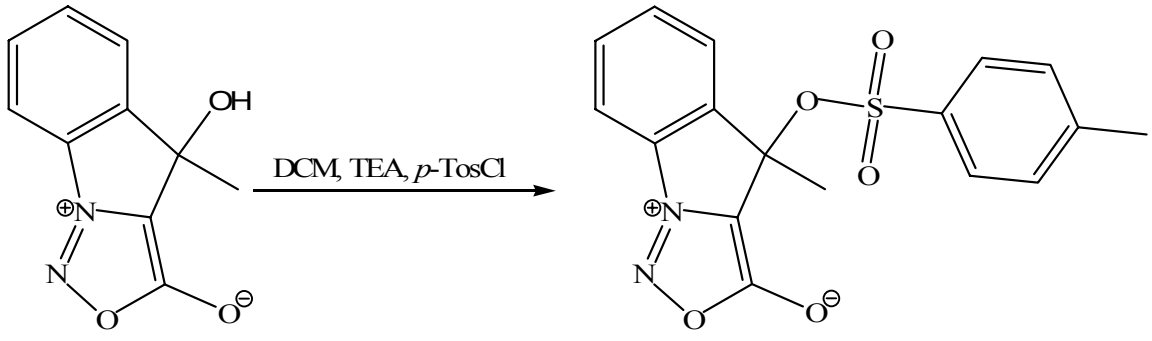
Now, having a stockpile of the 5-hydroxy-5-methylsydno[3,4-*a*]indole (**45**) in hand, one of the first thoughts was to investigate reactions of the alcohol moiety, especially those that might convert it into a potential leaving group. The first attempt to explore this potential involved using LDA, under the standard lithiation conditions (THF, -78ºCº, N_2), to abstract the proton from the alcohol and then adding methyl iodide as an electrophile (Scheme 9). Unfortunately, even after a considerable reaction time, this reaction resulted only in the recovery of the starting methyl sydnoindole **45**, not the anticipated 5-methoxy-5-methylsydno[3,4-*a*]indole (**85**). In a second attempt to effect the reaction, it was decided that perhaps the temperature had been too low to allow the desired reaction to take place. Accordingly, the reaction was re-run, this time at a temperature of 0ºC instead of the traditional -78ºC. Again, unfortunately, the result was that only the starting material was isolated.



Scheme 9: Projected reaction of the methyl sydnoindole **45** to form the target compound **85**

From the results of the previous reaction, it was apparent that the sydnoindoles were surprisingly stable, undoubtedly due to issues of steric hindrance. As another test of this apparent stability, it was decided to explore the conversion of the alcohol into a good

leaving group by the use of a reactive electrophile. It had been reported previously by Turnbull and Lowe[106] that treatment of 3-(2-acetylphenyl)sydnone oxime with methanesulfonyl chloride or *para*-toluenesulfonyl chloride in the presence of triethylamine (TEA) acting as a base, resulted in the oxygen of the oxime reacting with the sulfonyl compound to give a mesylate or tosylate leaving group. The above reaction had been run in dichloromethane (DCM), but with the difficulties in getting the methyl indole **45** to completely dissolve into DCM solution, for the reactions with **45**, acetone was initially used instead. The reaction protocol involved the *para*-toluenesulfonyl chloride being added slowly to a solution of the methyl sydnoindole **45** and TEA in acetone. The reaction yielded none of the desired product 5-tosyloxy-5-methylsydno[3,4-*a*]indole (**86**), and the starting methyl indole **45** was recovered. However, rather than conclude that the indole was completely unreactive, it was decided that the use of acetone may have hindered product formation. Accordingly, the methyl indole **45** was placed in DCM and, upon the addition of TEA, the methyl indole went into solution (Scheme 10). However, even with the use of DCM as the solvent, the same result occurred: no reaction. It was becoming increasingly clear that these sydnoindoles were very stable compounds and that future reactions upon them may not be possible.



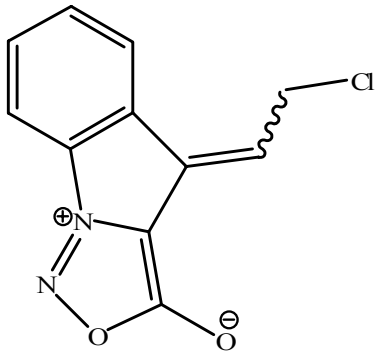
45 **86**

Scheme 10: Attempted reaction of the methyl sydnoindole **45** with *p*-TosCl to yield **86**

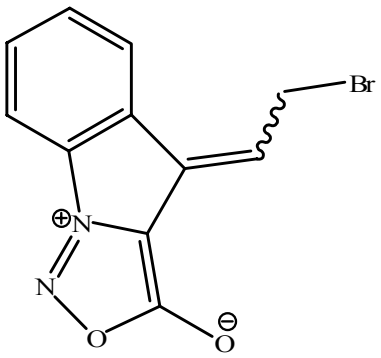
The last attempt at exploring the reactivity of these sydnoindoles was to test how the sydnoindole would act in the presence of an acid. Typically with sydnones, a reaction with acid would involve the cleavage of the sydnone ring; initiated by protonation at N-2. However, no studies had been undertaken with fused-ring sydnones, in general, and sydnoindoles in particular, to ascertain whether or not this pattern of reactivity would hold true in such circumstances. To test the acid-reactivity profile, the methyl sydnoindole **45** was used once again due to its abundance in our lab and ease of production. Thus, the methyl sydnoindole was added slowly to a vial containing concentrated hydrochloric acid and allowed to react for approximately two hours with two different workups: a) allowing the acid to evaporate off or b) neutralization of the reaction mixture followed by extraction. Unfortunately, once again, the results from this particular reaction were not promising since only miniscule quantities of another product were formed and the vast majority of the starting methyl sydnonindole was recovered. However, the preparation of the new 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**) provided some hope that a different reactivity profile might be forthcoming since the alcohol moiety is now allylic. Thus, the vinyl sydnoindole **81** was added to a vial of HCl, allowed to react for approximately two hours, the acid permitted to evaporate off and an extraction conducted after the addition of water and DCM. The reaction showed great promise as very little starting material was left behind and two products, one minor and one major, were obtained. Due to the overwhelming abundance of the major product, it was decided that this was to be the product of interest from the reaction. Column chromatography afforded the major product and testing of this product *via* IR showed an

interesting result since the alcohol was no longer present (as evidenced by the absence of OH str. at around 3300 cm^{-1}). To aid in the identification of this compound, ^{1}H and ^{13}C NMR spectroscopies were used. The results of the ^{1}H NMR showed a triplet integrating for a single hydrogen from 6.999-7.057 ppm as well as a doublet integrating for two hydrogens from 4.957-4.987 ppm. The ^{13}C NMR reconfirmed the fact that the sydnone was still present with a quarternary carbon present at 161.95 ppm representing the sydnone C-O, as well as a peak at 106.33 ppm representing the substituted sydnone C-4 position. It was also noted that there was a peak at 41.91 ppm, which represented the $-CH_2$ bonded to the Cl. Lacking in this NMR was the presence of the single carbon bridge bonded to an alcohol, which normally appears at 75.38 ppm in the vinyl indole starting material. With this information in hand, it was concluded that the structure of the product was that of **87**. This result, if correct, was surprising since no fused-ring sydnone with an sp^2 hybridized fused atom had been prepared previously and this conjecture was supported by the seeming instability of the sydnoindolone **74** developed in the present work. It seemed likely that if this compound resulted from the use of hydrochloric acid, a similar bromo compound **88** would follow from treatment with hydrobromic acid. Indeed, the product obtained from this reaction had almost identical ^{1}H NMR and ^{13}C NMR spectra to those for the putative chloro analog **87**. The obvious spectral differences were those, which might be anticipated for a change from a chlorine to a bromine. Thus, the terminal carbon attached to the bromine appeared at 30.31 ppm rather than at 41.91 ppm as in the new chlorinated compound. In principle, these compounds should exist as E and Z mixtures, however, none of the evidence gathered (TLC, NMR) indicates other than that these species are single entities. It was not possible through NMR data to

establish which stereoisomer was present, nor is it easy to explain why one stereoisomer would be favored, but it does seem to be the case. Further elucidiation will have to await the growth of crystals appropriate for X-ray Crystallography.



87



88

The proposed general mechanism for these reactions is shown in Figure 3. In this proposal, it seems likely that the first step is protonation of the alcohol, which then results in carbocation formation by expulsion of water. Resonance within the allylic system allows for the transfer of electrons to the carbocation, causing the terminal $-CH_2$ to have a partial positive charge, and enables the attack of the corresponding halide from the acid at the more accessible terminal location.

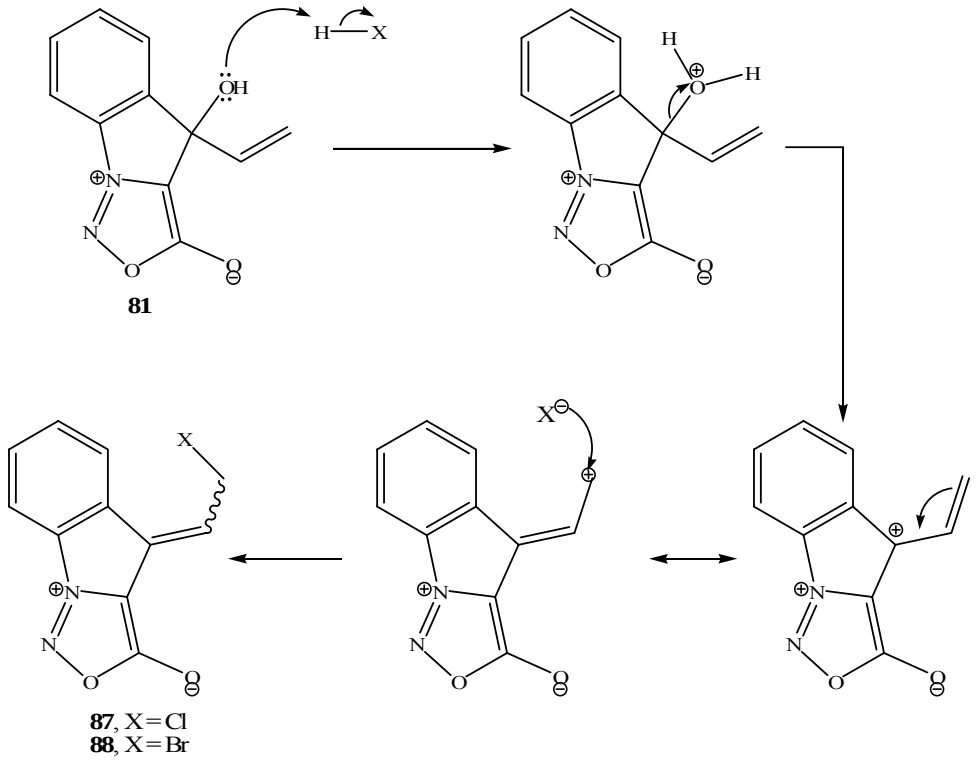
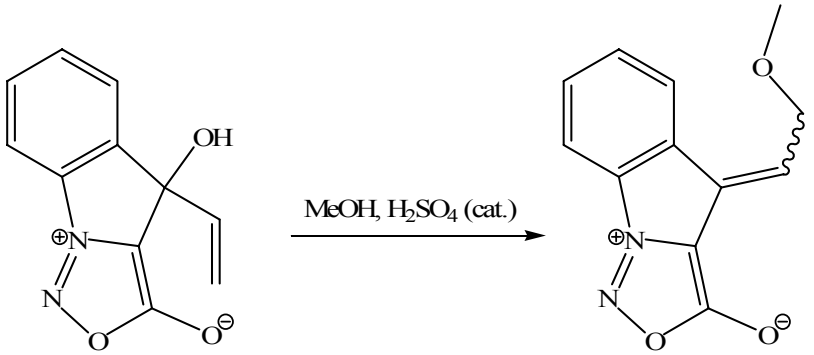


Figure 3: Proposed mechanism for reaction of the vinyl indole **81** with a general monoprotic acid.

Since 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**) showed promising reactivity, it seemed likely that other nucleophiles could be used to generate various interesting compounds similar to **87** and **88** (See Figure 3, replace X^- with Nu^-). For the first such experiment, it was elected to react the vinyl sydnone with an alcohol in the presence of a catalytic amount of sulfuric acid (the latter was chosen since it is a strong acid with a non-nucleophilic counterion). Two possible outcomes of the reaction were considered: a) where the methoxy group attaches to the bridging carbon, or b) where the methoxy group attaches to the terminal position (as shown with both HCl and HBr). After the reaction was complete, the product isolated (94% yield) appeared to have the same general spectral characteristics as those resulting from treatment of **81** with HCl or HBr and would, therefore, have the general structure **89** (Scheme 11). This compound should exist

as an E and Z mixture, but neither NMR spectra nor TLC showed a mixture, leading to the conclusion of one configuration. Once again, the reason for the attack of the nucleophile at the terminal position may be the result of steric hindrance toward attack at the bridging carbon. The success of this latter approach opens up the possibility of employing a wide range of different nucleophiles for similar transformations.



Scheme 11: Reaction of the vinyl sydnoindole **81** with MeOH and cat. H_2SO_4 to yield **89**

For future work, it may be possible to streamline the process leading to the sydnoindoles described above using a similar method that could potentially improve the yields. In this scenario, it should be possible to generate the 5-hydroxy-5-methylsydno[3,4-*a*]indole (**45**), 5-hydroxy-5-phenylsydno[3,4-*a*]indole (**79**) and 5-hydroxy-5-butylsydno[3,4-*a*]indole (**78**) without the use of LDA. Rather than including an additional step by using LDA to abstract the sydnone C-4 proton, it may be possible to increase the number of equivalents of the corresponding organolithium base (methyllithium, phenyllithium, and n-butyllithium) such that this base will abstract the sydnone ring proton to generate the anion, form the sydnoindolone **74** and then react as a nucleophile to afford the target sydnoindole. Of course, it is also possible that the

organolithium species will merely attack the ester moiety twice to yield a tertiary alcohol and, accordingly, this approach may need careful examination to afford success.

Further, with the discovery that the new 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**) is an attractive synthon for the preparation of interesting, novel fused-ring sydnones, further research can be performed upon this type of sydnoindole. The first order of business will be to increase the efficiency of generating the vinyl sydnoindole **81** directly from 3-phenysydnone **5** (R' = Ph, R = H). It might also be viable to generate other analogous sydnoindoles that have a carbon-carbon double bond present to test further the reactivity of these types of species.

In addition, reactions involving the 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**) could also be examined in future work. As described earlier, it should be possible to use other nucleophiles while using sulfuric acid as a catalyst to generate interesting fused-ring compounds. Ultimately, it may be possible to determine the conditions, if any exist, that would allow for the breakdown of the known fused-ring sydnoindoles, as well as these newly generated sydnones, to affect the release of NO from the sydnone ring system. Such compounds may then prove to be valuable antihypertensives.

Experimental

General Notes

All starting reagents and catalysts were purchased from commercial sources and used without further purification. Dry tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Where applicable (e.g. organolithium reagents), all glassware was flame-dried under an atmosphere of nitrogen prior to the use of dry reagents. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were acquired on a Mattson Genesis II FTIR. NMR spectra were acquired on a Bruker 300 MHz NMR. Samples were dissolved in deuterated dimethyl sulfoxide, deuterated chloroform or a mixture thereof. All lithiations were done in dry THF under an atmosphere of nitrogen. Unless specified all lithiations were performed at -78 ˚C, utilizing a dry ice/acetone slush bath. All bases utilized were assumed to be at the molarities listed on the reagent bottle.

Synthesis of the glycine **76** from methyl anthranilate (**75**)

To a stirred solution of methyl anthranilate (**75**) [11.5g, 76.1mmol] in water (60mL) was added a solution of bromoacetic acid (10.83g, 77.9mmol) and sodium acetate (10.95g, 133mmol) in water (60mL). The solution was heated at 60 ˚C for ~24 hours. After the allotted time, the brown powder-like product was filtered off and washed with water (200mL). The solid was then digested in ether and filtered to yield 7.256g (34.52mmol, 45%) of **76** as a white powder. The product was characterized by IR, TLC and melting point (176-178˚C) and matched known values.

IR (KBr): 3346 (N-H), 1722 (C=O), 1684 (C=O), 1601, 1433, 1255, 1127, 1081, 999, 855 cm^{-1}

Nitrosation of the glycine **76** to form N-(2-methoxycarbonyl)phenyl-N-nitrosoglycine **77**

To N-(2-methoxycarbonyl)phenylglycine (**76**) [7.256g, 34.52mmol] in dimethoxyethane (30mL) was added isoamyl nitrite (6.3mL, 46.9mmol) at 50ºC. The solution was allowed to stir under reflux at room temperature for 2 hours, after which time the solvent and excess isoamyl nitrite were evaporated off in a fume hood overnight. A dark red, brown solid resulted. The said solid was identified by TLC, but no further analysis was performed due to the potential health risks associated with the target N-(2-(methoxycarbonyl)phenyl)-N-nitrosoglycine (**77**).

Cyclization of **77** to yield 3-(2-methoxycarbonylphenyl)sydnone **73**

Due to the potential health risks of **77** the masses used are based on the assumption of its complete formation from **76**. To a solution of **77** (8.22g, 34.52mmol) in dichloromethane (20mL) at approximately 0˚C, trifluoroacetic anhydride (7mL, 74.05mmol) was added. The mixture was allowed to stir for 1 hour, after which time complete conversion of starting material had occurred by TLC. The solution was neutralized with aqueous sodium bicarbonate solution (5% w:v) and extracted with dichloromethane (3 x 50mL). The combined organic layers were dried and evaporated *in vacuo* to yield an orange-red solid material. Digestion with petroleum ether: ether (1:1) and recrystalization from dichloromethane: hexane gave a white solid, suitable for analysis. The compound was identical to known **73** by IR, TLC, ^{1}H NMR, ^{13}C NMR and melting point (98-100˚C)

IR (KBr): 3145 (syd C-H), 1745 (syd C=O), 1727 (C=O), 1434, 1290, 1145, 1079, 941, 763, 700 cm^{-1}

^{1}H NMR ($CDCl_3$): 3.85 (s, 3H), 6.59 (s, 1H, syd C-4), 7.59 (m, 1H), 7.80 (m, 2H), 8.16 (m, 1H) ppm

^{13}C NMR ($CDCl_3$): 168.70, 163.74 (syd C=O), 133.40, 132.53, 132.18, 127.14, 126.41, 97.70 (syd C-4), 53.14 ppm

Attempted formation of the sydno-(3-4-*a*)-indolone (**74**)

To a solution of the sydnone starting material **73** [0.200g, 0.9083mmol] in THF (40mL) at -78ºC was added 1.5 eq. LDA (0.91mL, 1.3625mmol) with stirring. After 1 hour, the reaction was quenched with water (50mL). The solution was allowed to evaporate to reduce the volume and extracted with dichloromethane (3 x 50mL). The combined extracts were dried with magnesium sulfate, filtered and the filtrate evaporated *in vacuo* to produce a dark blue oil. TLC showed a mixture of various products. Isolation of the target product by column chromatography was not achieved.

Modified attempt at the synthesis of the sydno-(3,4-*a*)-indolone (**74**) using higher dilution

To a solution of the sydnone starting material (**73**) [0.200g, 0.9083mmol] in THF (100mL) at -78ºC was added 1.5 eq. LDA (0.91mL, 1.3625mmol). After 1 hour, the reaction was quenched with water (50mL). The solution was allowed to evaporate to reduce the volume and extracted with dichloromethane (3 x 50mL). The combined extracts were dried with magnesium sulfate, filtered and the filtrate evaporated *in vacuo* to afford a dark blue oil. Again, TLC examination showed a mixture of various products

and column chromatography did not afford the target product or any characterizable substance.

"Trapping" of the sydnoindolone **74** for the synthesis of the 5-hydroxy-5-butylsydno[3,4-*a*]indole (**78**) and 5-hydroxy-5-methylsydno[3,4-*a*]indole (**45**)

To a solution of the sydnone starting material **73** [0.200g, 0.9083mmol] in THF (100mL) at -78ºC was added 1.5 eq. LDA (0.91mL, 1.3625mmol). After 1 hour, the corresponding organolithium base (1.5 equiv) was added. After 1 hour, the reaction was quenched with water (50mL) and the solution was allowed to evaporate to reduce the volume and extracted with dichloromethane (3 x 50mL). The combined extracts were dried with magnesium sulfate, filtered and the filtrate evaporated *in vacuo*. Column chromatography (silica gel, dichloromethane: acetone as eluant) yielded the corresponding target sydnoindoles, which were analyzed by IR, ^{1}H NMR, ^{13}C NMR, and m.p.

Using methyl lithium (0.90mL, 1.5M) in the general procedure gave 5-hydroxy-5-methylsydno[3,4-*a*]indole (**45**): (0.061g, 0.2997mmol, 33% yield, m.p. 181-182°C, lit[92] m.p. 184-187°C)

IR (KBr): 3336 (-OH), 1721 (syd C=O), 1483, 1400, 1137, 1103, 1006, 852, 769, 684 cm^{-1}

^{1}H NMR (d_6-DMSO): 1.73 (s, 3H), 6.31 (s, 1H, OH), 7.72 (m, 3H), 7.96 (d, 1H) ppm

^{13}C NMR (d_6-DMSO): 162.94 (syd C=O), 145.89, 132.90, 132.36, 129.99, 124.95, 114.16, 112.00 (syd C-4), 72.57 (C-OH), 23.24 ppm

Using butyl lithium (0.85mL, 1.6M) in the general procedure gave 5-hydroxy-5-butylsydno[3,4-*a*]indole (**78**): (0.022g, 0.0908mmol, 10% yield, oil)

IR (NaCl): 3352 (-OH), 2926 (alkyl C-H), 1740 (syd C=O), 1673, 1619, 1465, 1276, 1079, 762, 734 cm^{-1}

^{1}H NMR (d_6-DMSO): 0.83 (t, 3H), 1.02 (d, 1H), 1.27 (m, 3H), 1.90 (m, 1H), 2.16 (m, 1H), 6.28 (s, 1H, OH), 7.71 (m, 3H), 7.98 (d, 1H) ppm

^{13}C NMR (d_6-DMSO): 164.64 (syd C=O), 144.75, 133.65, 132.36, 130.08, 125.32, 114.43, 111.42 (syd C-4), 76.98 (C-OH), 38.34, 26.73, 22.82, 13.69 ppm

Modification of the trapping procedure for the improved synthesis of 5-hydroxy-5-methylsydno[3,4-*a*]indole (**45**) and 5-hydroxy-5-butylsydno[3,4-*a*]indole (**78**), and for the synthesis of 5-hydroxy-5-phenylsydno[3,4-*a*]indole (**79**)

To a solution of the sydnone starting material **73** [0.200g, 0.9083mmol] in THF (100mL) at -78ºC was added 1.5 eq. LDA (0.91mL, 1.3625mmol). After 10 minutes, the corresponding organolithium base (1.5 equiv) was added. After 1 hour, the reaction was quenched with water (100mL). The solution was allowed to evaporate to reduce the volume and extracted with dichloromethane (3 x 50mL). The combined extracts were dried with magnesium sulfate, filtered and the filtrate evaporated *in vacuo*. Column chromatography (silica gel, dichloromethane: acetone as eluant) yielded the corresponding target sydnoindoles. Sydnoindoles **45** and **78** were compared *via* TLC evidence to those previously generated. Sydnoindole **79** was analyzed with IR, ^{1}H NMR, ^{13}C NMR, and m.p. The methyl indole **45** was generated in a yield of 44% (0.82g,

0.3997mmol) and the butyl indole **78** was generated in a 15% yield (0.034g, 0.1362mmol).

Using phenyl lithium (0.75mL, 1.8M) in the general procedure gave 5-hydroxy-5-phenylsydno[3,4-*a*]indole (**79**): (0.061g, 0.2771mmol, 25% yield, m. p. 153-155ºC, lit[92] m.p. 158-160°C)

IR (KBr): 3340 (OH), 1747 (syd C=O), 1731, 1481, 1376, 1197, 1168, 1047, 1024, 919, 869 cm^{-1}

^{1}H NMR (d_6-DMSO): 7.042 (s, 1 H, OH), 7.37 (m, 3H), 7.54 (m, 3H), 7.69 (m, 3H) ppm

^{13}C NMR (d_6-DMSO): 162.57 (syd C=O), 145.81, 138.73, 132.99, 132.70, 130.28, 128.57, 128.35, 126.11, 125.43, 114.53, 111.64 (syd C-4), 76.53 (C-OH) ppm

General procedure for synthesis of the 5-hydroxy-5-methylsydno[3,4-*a*]indole (**45**), 5-hydroxy-5-phenylsydno[3,4-*a*]indole (**79**), and 5-hydroxy-5-butylsydno[3,4-*a*]indole (**78**) using LHMDS

To a solution of the sydnone starting material **73** [0.200g, 0.9083mmol] in THF (100mL) at -78ºC was added 1.5 eq. LHMDS (1.36mL, 1.36mmol). After 20 minutes, the corresponding organolithium base (1.5 equiv) was added. After 1 hour, the reaction was quenched with water (100mL). The solution was allowed to evaporate to reduce the volume and extracted with dichloromethane (3 x 50mL). The combined extracts were dried with magnesium sulfate, filtered and the filtrate evaporated *in vacuo*. Column chromatography (silica gel, dichloromethane: acetone as eluant) yielded the

corresponding target sydnoindole. The compounds were compared *via* TLC evidence to previously synthesized sydnoindoles. Yields of sydnoindoles **45**, **79**, and **78**, were synthesized in yields of 12%, 8%, and 6%, respectively.

General procedure for the synthesis of the 5-hydroxy-5-phenylsydno[3,4-*a*]indole (**79**), 5-hydroxy-5-ethylsydno[3,4-*a*]indole (**80**), and 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**) using Grignard reagents

To a solution of the sydnone starting material **73** [0.200g, 0.9083mmol] in THF (100mL) at -78ºC was added 1.5 eq. LDA (0.91mL, 1.3625mmol). After 10 minutes, the corresponding Grignard reagent (1.1 equiv.) was added. After 1.5 hours, the reaction was quenched with water (100mL). The solution was allowed to evaporate to reduce the volume and extracted with dichloromethane (3 x 50mL). The combined extracts were dried with magnesium sulfate, filtered and the filtrate evaporated *in vacuo*. Column chromatography (silica gel, dichloromethane: acetone as eluant) yielded the corresponding target sydnoindole. Sydnoindole **79** [from phenylmagnesium bromide (1.0mL, 1.0M)] was generated in a 23% yield (0.056g, 0.2089mmol) and matched previously synthesized material by TLC evidence. Sydnoindoles **80** and **81** were analyzed *via* TLC, IR, ^{1}H NMR and ^{13}C NMR.

Using ethylmagnesium bromide (1.0mL, 1.0M) in the general procedure gave the 5-hydroxy-5-ethylsydno[3,4-*a*]indole (**80**): (0.029 g, 0.1329mmol, 15% yield, m. p. 144-146 ºC, lit[92] m.p. 152-153°C)

IR (KBr): 3326 (OH), 2978, 1729 (syd C=O), 1485, 1425, 980, 774 cm^{-1}

^{1}H NMR (d_6-DMSO): 0.98 (t, 3H), 1.98 (m, 1H), 2.25 (m, 1H), 6.36 (s, 1H, OH), 7.77 (m, 3H), 8.03 (d, 1H) ppm

^{13}C NMR (d_6-DMSO): 163.40 (C=O), 145.20, 133.15, 132.37, 120.06, 125.17, 114.16, 111.19 (syd C-4), 76.76 (C-OH), 30.37 (CH_2), 8.88 (CH_3) ppm

Using vinylmagnesium bromide (1.0mL, 1.0M) in the general procedure gave the 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**): (0.028g, 0.1295mmol, 14% yield, 142-144ºC)

IR (KBr): 3344 (O-H), 1736 (C=O), 1621, 1483, 1292, 1175, 987, 957, 842 cm^{-1}.

^{1}H NMR (d_6-DMSO): 5.30 (d, 1H), 5.56 (d, 1H), 6.12 (overlapped doublet of doublets, 1H), 6.67 (s, 1H, OH), 7.71 (m, 3H), 8.01 (d, 1H) ppm

^{13}C NMR (d_6-DMSO): 162.91 (C=O), 144.40, 135.04, 132.99, 132.53, 130.29, 125.76, 116.02, 114.38, 110.21 (syd C-4), 75.38 (C-OH) ppm

Elemental Anlysis: $C_{11}H_8N_2O_3$ (MW: 216.19) Calculated: C: 61.11; H: 3.73; N: 12.96; Found: C: 60.82; H: 3.81; N:12.76

Alternate route to the synthesis of 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**) from 3-phenylsydnone **5** (R' = Ph, R = H)

To a stirred solution of the 3-phenylsydnone (**5**, R' = Ph, R = H) [0.200g, 1.2334mmol) in THF (100mL) at -78ºC was added 2.2 eq. n-butyllithium (1.7mL, 2.72mmol). After 20 minutes, 1.5 eq. of methyl acrylate (0.17mL, 1.8858mmol) was added and allowed to react for ~1.5 hours. At this time, the reaction was quenched with water (100mL) and the solution was allowed to evaporate to a reduced volume. Then, the solution was extracted with dichloromethane (3 x 50mL) and the combined layers were dried with magnesium sulfate, filtered and the filtrate evaporated *in vacuo* to yield a yellow oil. Column

chromatography (silica gel, dichloromethane: acetone as eluent) yielded the target vinyl indole **81** in a yield of 15% (0.040g, 0.1850mmol). The product was compared *via* TLC and IR to previously generated samples.

Attempted Wittig reaction to form **82** from 3-(2 methoxycarbonylphenyl)sydnone (**73**)

To a solution of the sydnone starting material **73** (0.200g, 0.9083mmol) in THF (100mL) was added 1.5 eq. of LDA (0.91mL, 1.3625mmol). After 10 minutes, methyltriphenylphosphonium bromide (1.1 eq., 0.357, 0.9991mmol) and another 1.5 eq. of LDA was added. The reaction was allowed to run for 4 hours, at which time it was quenched with water (100mL). The solution was allowed to evaporate down to reduce the volume of THF, extracted with dichloromethane (3 x 50mL), the combined extracts dried with magnesium sulfate, filtered and the filtrate evaporated *in vacuo*. The resultant oil was separated *via* column chromatography (silica gel, dichloromethane: acetone as eluant) to yield a dark-brown solid. IR and ^{1}H NMR spectral analysis showed that the compound was **83** and not the target **82**. The product was generated in a yield of 5% (0.013g, 0.0454mmol). Repetition of the experiment without the Wittig reagent produced similar results. Neither the reaction nor its product was further tested.

IR (NaCl): 3151(syd C-H), 1763 (syd C=O) 1630, 1445, 1375, 1344, 1208, 1162, 1095, 1033, 940, 773 cm^{-1}.

^{1}H NMR ($CDCl_3$): 1.01 (d, 3H), 1.12(d, 3H), 1.43(d, 3H), 1.52 (d, 3H), 3.54 (m, 2H), 6.79(s, 1H, syd C-H), 7.45 (s, 1H), 7.66 (m, 3H) ppm

Intramolecular lithiation of 3-(2-acetylphenyl)sydnone (**84**) to form 5-hydroxy-5-methylsydno[3,4-*a*]indole (**45**)

To a solution of 3-(2-acetylphenyl)sydnone (**84**) [0.200g, 0.9795mmol] in THF (100mL) at -78˚C was added 1.5 eq. LDA (0.97mL, 1.4693mmol). After 1 hour, the reaction was quenched with water (100mL) and allowed to evaporate to 100mL. The reduced mixture was extracted with dichloromethane (3 x 50mL), and the combined extracts were dried with magnesium sulfate, filtered and the filtrate evaporated *in vacuo* to yield a tan solid. Characterization of the compound by IR, ^{1}H NMR and melting point comparisons with those of an authentic sample showed the compound to be the fused-ring sydnoindole **45** (0.172g, 0.8424mmol, 86%).

Attempted synthesis of 5-methoxy-5-methylsydno[3,4-*a*]indole (**85**) from the methyl sydnoindole **45**

To a solution of the methyl sydnoindole **45** (0.100g, 0.4898mmol) in THF (50mL) at -78ºC was added 1.5 eq. LDA (0.5mL, 0.7347mmol). After 20 minutes, 1.2 equiv MeI (37.00µL, 0.5930mmol) was added and allowed to react for 1.5 hours. At this time, the reaction was quenched with water (50mL) and the solution was allowed to evaporate down to reduce the volume. The solution was then extracted with dichloromethane (3 x 50mL) and the combined extracts were dried with magnesium sulfate, filtered and the filtrate evaporated *in vacuo*. TLC and IR showed recovery of the starting material **45** and no additional products were discovered. Subsequent reaction at a temperature of 0ºC rather than -78ºC gave similar results.

Attempted synthesis of 5-tosyloxy-5-methylsydno[3,4-*a*]indole (**86**) from 5-hydroxy-5-methylsydno[3,4-*a*]indole (**45**)

To a stirred solution of the methyl sydnoindole **45** (0.200g, 0.9083mmol) in acetone/triethylamine (5mL/0.5mL) was added the electrophile *p*-toluenesulfonylchloride (0.200g) in small portions. The reaction was allowed to run for ~12 hours, at which time the solution was poured into water (20mL) and dichloromethane (3 x 10mL) was added. The combined organic layers were separated and washed successively with hydrochloric acid (10%, 2 x 10mL), aqueous sodium bicarbonate (10 %, 2 x 10mL), and brine (10mL). The dried extract was evaporated *in vacuo*. IR and TLC evidence showed the starting methyl sydnoindole **45** was recovered as well as the *p*-toluenesulfonylchloride. No additional products resulted.

Attempted synthesis of 5-tosyloxy-5-methylsydno[3,4-*a*]indole (**86**) from the methyl sydnoindole **45** in dichloromethane

To a stirred solution of the methyl sydnoindole **45** (0.200g, 0.9083mmol) in dichloromethane/triethylamine (5mL/0.5mL) was added the electrophile *p*-toluenesulfonylchloride (0.200g) in small portions. The reaction was allowed to run for ~12 hours, at which time the solution was poured into water (20mL). The separated organic layer was washed successively with hydrochloric acid (10%, 2 x 10mL), aqueous sodium bicarbonate (10 %, 2 x 10mL), and brine (10mL). The dried extract was evaporated *in vacuo*. IR and TLC evidence showed the starting methyl sydnoindole 45 was recovered as well as the *p*-toluenesulfonylchloride. No additional products resulted.

Reaction of methyl sydnoindole **45** with HCl

The sydnoindole **45** [0.100g, 0.4898mmol] was added to a vial of concentrated HCl (~6mL) and allowed to react for 2 hours. At this time, the HCl was allowed to evaporate off. Water (15mL) was then added to the mixture and the solution was extracted with dichloromethane (3 x 20mL). The extracted layers were combined, dried with magnesium sulfate, filtered, and the filtrate evaporated *in vacuo*. TLC showed the recovery of the starting sydnoindole **45** and very few additional products. IR confirmed the significant recovery of the starting material. Subsequent reaction with a modified workup of neutralization of the initial reaction rather than allowing the HCl to evaporate resulted in similar results.

Reaction of 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**) with HCl

The vinyl sydnoindole **81** [0.028g, 0.1295mmol] was added to a vial of concentrated HCl (~6mL) and allowed to react for 2 hours. At this time, the HCl was allowed to evaporate off. Water (15mL) was then added to the mixture and the solution was extracted with dichloromethane (3 x 20mL). The extracted layers were combined, dried with magnesium sulfate, filtered, and the filtrate evaporated *in vacuo*. TLC showed the conversion of the starting material **81**. IR and NMR showed the structure of the synthesized material to be that of **87**. The yield from the reaction was 88% [0.027g, 0.1151mmol, m.p. 132-134 °C (dec. before melting)].

IR (KBr): 3039 (=C-H), 1767 (syd C-O), 1736, 1641, 1260, 1200, 1099, 1021, 682 cm^{-1}

^{1}H NMR (d_6-DMSO): 4.97 (d, 2H), 7.03 (t, 1H), 7.76 (m, 2H), 8.09 (d, 1H), 8.26 (d, 1H) ppm

^{13}C NMR (d_6-DMSO): 161.95 (C=O), 132.85, 132.67, 131.56, 130.40, 124.44, 123.57, 123.54, 114.24, 106.33 (syd C-4), 41.91 (CH_2-Cl) ppm

Reaction of 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81)** with HBr

The vinyl sydnoindole **81** [0.036g, 0.1665mmol] was added to a vial of concentrated HBr (~6mL) and allowed to react for 2 hours. At this time, the HCl was allowed to evaporate off. Water (15mL) was then added to the mixture and the solution was extracted with dichloromethane (3 x 20mL). The extracted layers were combined, dried with magnesium sulfate, filtered, and the filtrate evaporated *in vacuo*. TLC showed the conversion of the starting material **81**. IR and NMR showed the structure of the synthesized material to be that of **88**. Yield from the reaction was 73% (0.034g, 0.1218mmol, m. pt. 118-120ºC (dec. before melting)).

IR (KBr): 3042 (=C-H), 1743 (syd C-O) 1730, 1634, 1276, 1203, 1098, 1021, 682 cm^{-1}

^{1}H NMR (d_6-DMSO): 4.91 (d, 2H), 7.11 (t, 1H), 7.75 (m, 2H), 8.07 (d, 1H), 8.24 (d, 1H) ppm

^{13}C NMR (d_6-DMSO): 161.96 (C=O), 132.83, 132.64, 131.58, 130.43, 124.41, 124.02, 123.58, 114.58, 106.46 (syd C-4), 30.31 (CH_2-Br) ppm

Reaction of 5-hydroxy-5-vinylsydno[3,4-*a*]indole (**81**) with MeOH and cat. H_2SO_4 to form **89**

The vinyl sydnoindole **81** [0.034g, 0.1480mmol] was added to a vial of methanol (~8mL). A catalytic amount of sulfuric acid (~4-5 drops) was added and allowed to react for 2 hours. At this time, the methanol was evaporated *in vacuo*. The solid was re-

dissolved in dichloromethane (15mL) and the solution was neutralized with aqueous sodium bicarbonate (5% w:v). The solution was then extracted with dichloromethane (3 x 20mL). The extracted layers were combined, dried with magnesium sulfate, filtered, and the filtrate evaporated *in vacuo*. TLC showed the conversion of the starting material **81**. IR and NMR data indicated the structure of the synthesized material to be that of **89**. The yield from the reaction was 94% (0.032g, 0.1390mmol m. p. 108-111ºC).

IR (KBr): 3094 (=C-H), 1760 (syd C-O), 1734, 1645, 1185, 1118, 1088, 1023, 1011, 860, 686 cm^{-1}

^{1}H NMR ($CDCl_3$): 3.385 (s, 3H, -OMe), 4.69 (d, 2H), 6.58 (t, 1H), 7.56 (m, 2H), 7.71 (t, 2H) ppm

^{13}C NMR ($CDCl_3$): 162.67 (C=O), 133.74, 132.94, 131.23, 129.65, 126.18, 123.46, 122.52, 113.98, 106.85 (syd C-4), 70.13 (CH_2), 58.54 (CH_3) ppm

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